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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 14

Application Number: 09/991,212
Filing Date: November 16, 2001
Appellant(s): LAL ET AL.

Terence P. Lo
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 15, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellants' statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellants' statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that all claims on appeal stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Bork *Genome Res* 10:398-400

Brenner *Trends Genet* 15:132-133

Brenner et al. *PNAS* 95:6073-6078*

Broun et al. *Science* 282:1315-1317

Brown et al. (US Patent 5,807,522)*

Lashkari et al. *PNAS* 94:8945*

Gerlt et al. (*Genome Biol* 1:reviews0005.1-0005.10)

Murzin et al. *J Mol Biol* 247:536-540

Nuwaysir et al. *Mol Carcinogen* 24:153*

Vrljic et al. *J Mol Microbiol Biotechnol* 1:327-336

Rockett et al. *Environ Health Perspectives* 107:681*

Rockett et al. *Xenobiotica* 29:655*

Scott et al. *Nat Genet* 21:440-443

Seffernick et al. *J Bacteriol* 183:2405-2410

Shattuck-Eidens et al. (US Patent 5,693,473)

Steiner et al. *Tox Lett* 112-113:467*

Tenenhouse et al. *Am J Physiol* 275:F527-F3 van de Loo et al. *PNAS* 92:6743-6747

* indicates reference cited by appellant

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Utility Rejection Under 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 3-7, 9-10, 12-13, 46, 48, and 57-58 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or well-established utility. Claims 3-6, 12-13, and 57-58 are drawn to an isolated polynucleotide encoding SEQ ID NO:1 or the polynucleotide of SEQ ID NO:2 and variants and fragments thereof. Claim 7 is drawn to a cell transformed with the recombinant polynucleotide of claim 6. Claims 9-10 are drawn to a method of producing a polypeptide of SEQ ID NO:1 and variants and fragments thereof. Claim 46 is drawn to a microarray comprising the polynucleotide of claim 13. Claim 48 is drawn to an array comprising a polynucleotide comprising a fragment of the polynucleotide of claim 12.

The polypeptide of SEQ ID NO:1 encoded by SEQ ID NO:2 (also referred to as NAPTR in the specification) is disclosed as being a sodium-phosphate cotransporter (see, e.g., page 10 of the specification). This assigned function appears to be based on an asserted 48% sequence identity to a human renal sodium phosphate transport protein (NPT1) and an asserted 29% amino acid sequence identity to rat brain-specific sodium dependent inorganic phosphate cotransporter (see pages 10-11 of the specification). However, as NAPTR shares a relatively low level of amino acid identity to NPT1 and rat brain-specific sodium dependent inorganic phosphate cotransporter, one of ordinary skill in the art would recognize that the disclosed structural characteristics are insufficient to ascertain the function of NAPTR. The specification does not disclose any working examples to demonstrate the polynucleotide of SEQ ID NO:2 and NAPTR exhibit activities similar to other sodium-phosphate transporter proteins and the skilled artisan would not be able to categorize the polynucleotide and polypeptide of the instant application as a

transporter protein. In the instant case, while sequence homology may be used to *predict, i.e., suggest,* the function of an encoded polypeptide, without functional characterization of the protein, there is no way to determine its actual biological activity. The prior art supports the examiner's argument. For example, Bork teaches gene annotation, i.e., predicting the function of an encoded polypeptide based on amino acid sequence identity to another polypeptide, by sequence database searches has a considerable error rate (page 399) and Brenner (*Trends Genet* 15:132-133; hereafter referred to as "Brenner (1999)") teaches that it is impossible to determine the reliability of a functional assignment of a protein without verification by laboratory experiments (page 132, left column). Also, Scott et al. (*Nat Genet* 21:440-443) teach a polypeptide that has 45% sequence identity (it is noted that NAPTR similarly shares 48% identity with NPT1) with a human sulfate transporter and that, based on structural homology has been proposed to function as a sulfate transporter (page 440, left column, abstract). However, an empirical analysis of the protein revealed that the protein is not a sulfate transporter and is actually a chloride-iodide transport protein (page 441, left column, third full paragraph). Scott et al. conclude that, "[t]hese results underscore the importance of confirming the function of newly identified gene products even when database searches reveal significant homology to proteins of known function" (page 441, left column, third full paragraph). While NAPTR may exhibit amino acid sequence identity with other sodium-phosphate cotransport proteins, without functional characterization of NAPTR, there is no way to determine whether the protein has sodium-phosphate transport activity. This further characterization, however, is part of the act of invention and, until it has been undertaken, the claimed invention is incomplete. In this case, one of ordinary skill in the art would recognize that further experimentation is required to determine whether NAPTR has sodium-phosphate transport activity.

Even assuming *arguendo* that NAPTR has sodium-phosphate transport activity, neither the prior art nor the specification teaches the biological significance of the claimed polynucleotides. The specification discloses, "[t]he discovery of proteins related to human renal sodium phosphate transport protein, and the polynucleotides encoding them, satisfies a need in the art by providing new compositions useful in diagnosis and treatment of diseases associated with increased or decreased phosphate levels" (page 2, bottom). While SEQ ID NO:2 is asserted to have been identified from a sample of human brain

tumor tissue (page 10, bottom of the instant specification), there is no disclosure in the specification that this nucleic acid is expressed only in tumor or brain tumor tissue, nor does the specification disclose that the claimed nucleic acid has altered expression in tumor or brain tumor tissue as compared to normal tissue. Furthermore, the specification fails to provide guidance for treating or diagnosing any *specific* disease that may be associated with altered phosphate levels. Absent such a disclosure, the claimed invention is incomplete and fails to provide a specific benefit in currently available form.

Therefore, one of ordinary skill in the art would recognize that further experimentation is required to ascertain the function of NAPTR and/or its biological significance in order to establish a "real world" use for the polynucleotide of SEQ ID NO:2. This type of utility is not considered a "substantial utility". See e.g., *Brenner v. Manson,* 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). The specification must teach a skilled artisan how to use what is claimed and not merely provide a blueprint for further experimentation in order for an artisan to identify a use for the claimed invention. As stated in *Brenner v. Manson*, 383 U.S. 519 535-536, 148 USPQ 689, 696 (1966), "[a] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion". Here the specification fails to provide a specific benefit in currently available form for the claimed polynucleotide as the claimed polynucleotide is suitable only for additional research in order that one of ordinary skill in the art may determine the biological function and/or significance of the claimed polynucleotides.

Regarding a specific utility, appellant asserts various utilities for the claimed polynucleotide and array including, e.g., use as a hybridization probe, for protein expression, and for therapeutic and diagnostic purposes. However, none of these asserted utilities is a specific utility for the claimed polynucleotide and array. The use of a polynucleotide for protein expression and hybridization is not specific as *any* polynucleotide has such utilities. Furthermore, regarding the use of the claimed polynucleotide as a therapeutic or for diagnostic purposes, it is noted that the specification fails to disclose a nexus between the claimed polynucleotide and a *specific* disease state such that the polynucleotide is useful for diagnosing or therapeutically treating a disease state or condition. Therefore, the asserted utilities are not specific to the claimed polynucleotide and are instead general utilities that would be applicable to the broad class of polynucleotides.

For the reasons stated above, the claimed polynucleotide has no specific and substantial utility.

Written Description Rejection Under 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 6-7, 9, 12-13, 46, 48, and 57-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention.

Claim 3 (claims 6, 7, and 9 dependent therefrom) is drawn (in relevant part) to a genus of isolated polynucleotides encoding a polypeptide comprising a naturally occurring amino acid sequence that is at least 90% identical to SEQ ID NO:1. Claim 12 is drawn (in relevant part) to a genus of isolated polynucleotides comprising a naturally occurring sequence at least 90% identical to SEQ ID NO:2, complete complements thereof, and RNA equivalents thereof. Claim 13 (claim 46 dependent therefrom) is drawn (in relevant part) to a genus of isolated polynucleotides comprising at least 20 contiguous nucleotides of: a polynucleotide consisting of nucleotides 1183-1454 of SEQ ID NO:2, a polynucleotide consisting of a naturally-occurring polynucleotide that is 90% identical to nucleotides 1183-1454 of SEQ ID NO:2; complete complements thereof, and RNA equivalents thereof. Claim 48 is drawn to an array comprising a genus of nucleic acid molecules comprising a polynucleotide completely complementary to at least 30 contiguous nucleotides of a polynucleotide of claim 12. Claim 57 limits the polynucleotide of claim 12 to (in relevant part) a genus of isolated polynucleotides comprising a naturally occurring sequence at least 95% identical to SEQ ID NO:2, complete complements thereof, and RNA equivalents thereof. Claim 58 limits the polynucleotide of claim 13 to (in relevant part) a genus of isolated polynucleotides comprising at least 60 contiguous nucleotides of: a polynucleotide consisting of nucleotides 1183-1454 of SEQ ID NO:2, a polynucleotide consisting of a naturally-occurring

polynucleotide that is 90% identical to nucleotides 1183-1454 of SEQ ID NO:2; complete complements thereof, and RNA equivalents thereof.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the appellant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the genus of claimed polynucleotides, i.e., the polynucleotide of SEQ ID NO:2, encoding a polypeptide asserted to have phosphate transport activity. The specification fails to describe any additional representative species of the claimed genus either by chemical structure or function. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the claimed genus of polynucleotides encompasses species that are widely variant in both structure and function, including (but not limited to) genomic sequences, allelic variants, and nucleic acid variants encoding polypeptides having function other than the asserted phosphate transport activity, e.g., non-functional polypeptides and polypeptides having activity other than the asserted phosphate transport activity. As such, the disclosure of the single representative species of SEQ ID NO:2 is insufficient to be representative of the attributes and features of *all* species encompassed by the claimed genus of polynucleotides. Given the lack of description of a representative number of polynucleotides, the specification fails to sufficiently describe the claimed invention in such full, clear,

concise, and exact terms that a skilled artisan would recognize that appellant was in possession of the claimed invention.

Also, regarding claims 3, 12, 13, 57, and 58, the claims recite the term "naturally occurring", which encompasses allelic variants of the nucleic acid of SEQ ID NO:2. The specification defines an "allelic sequence" (see page 12 of the instant specification) as an alternative form of the gene which may result in at least one mutation in the nucleic acid sequence. Alleles may result in altered mRNAs or polypeptides whose structure or function may or may not be altered. This definition does not provide any specific information about the structure of naturally occurring variants of SEQ ID NO:2 (e.g., the regions within which mutations are likely to occur) nor discloses any function for naturally occurring variants. There is no description of the mutational sites that exist in nature, and there is no description of how the structure of SEQ ID NO:2 relates to the structure of any naturally occurring alleles. The general knowledge in the art concerning alleles dose not provide any indication of how one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art structure of one does not provide guidance to the structure of others. The species of polynucleotides comprising the claimed genus is large and highly variable with potentiality of encoding many different proteins. Therefore, many functionally unrelated polynucleotides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus (i.e., SEQ ID NO:2) which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the appellant had possession of the claimed invention at the time the instant application was filed.

Scope of Enablement Rejection Under 35 USC § 112, First Paragraph

Even if appellant demonstrates the polynucleotide encoding SEQ ID NO:1 has a specific and substantial or well-established utility, the following rejection still applies. Claims 3, 6, 7, 9, 12, 13, 46, 48, 57, and 58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide encoding SEQ ID NO:1 and an array comprising a polynucleotide encoding SEQ ID NO:1, does not reasonably provide enablement for *all* isolated polynucleotides encoding a

polypeptide comprising a naturally occurring amino acid sequence that is at least 90% identical to SEQ ID NO:1; *all* isolated polynucleotides comprising a naturally occurring sequence at least 90% or 95% identical to SEQ ID NO:2, complete complements thereof, and RNA equivalents thereof; *all* isolated polynucleotides comprising at least 20 or 60 contiguous nucleotides of: a polynucleotide consisting of nucleotides 1183-1454 of SEQ ID NO:2, a polynucleotide consisting of a naturally-occurring polynucleotide that is 90% identical to nucleotides 1183-1454 of SEQ ID NO:2; complete complements thereof, and RNA equivalents thereof; and an array comprising *all* nucleic acid molecules comprising a polynucleotide completely complementary to at least 30 contiguous nucleotides of a polynucleotide of claim 12. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that the claimed or recited polynucleotides require undue experimentation for a skilled artisan to make and/or use. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). Those Factors most relevant to the instant rejection are addressed below.

- The breadth of the claims: the claims are so broad as to encompass *all* polynucleotides encoding a polypeptide comprising a naturally-occurring amino acid sequence that is at least 90 % identical to SEQ ID NO:1 (claim 3), *all* polynucleotides comprising a naturally-occurring polynucleotide that is at least 90% or 95% identical to SEQ ID NO:2, complements thereof, and RNA equivalents thereof, respectively (claim 12), *all* polynucleotides comprising at least 20 or 60 contiguous nucleotides of: nucleotides 1183-1454 of SEQ ID NO:2 or a complement thereof, a naturally-occurring polynucleotide that is at least 90 % identical to nucleotides 1183-1454 of SEQ ID NO:2 or a complement thereof, and RNA equivalents thereof (claims 13 and 58), and an array comprising *all* nucleic acid molecules comprising a first oligonucleotide or polynucleotide that is completely complementary to least 30 contiguous nucleotides of a target

polynucleotide of claim 12 (claim 48). The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claims. In this case, the disclosure is enabling only for a polynucleotide encoding SEQ ID NO:1 and an array comprising a polynucleotide encoding SEQ ID NO:1.

- The lack of guidance and working examples: The specification provides only a single working example of the claimed polynucleotide, i.e., SEQ ID NO:2 and only a single working example of a polypeptide encoded thereby, i.e., SEQ ID NO:1. These working examples fail to provide the necessary guidance for making and/or using the entire scope of recited polynucleotides. The specification fails to provide guidance regarding those nucleotides of SEQ ID NO:2 that may be altered by substitution, addition, insertion, and/or deletion with an expectation of maintaining the desired activity or utility. Furthermore, the specification fails to provide guidance as to how to use those variant nucleic acids – both naturally and non-naturally occurring – that encode polypeptides having activities other than the desired activity, e.g., nucleic acids encoding non-functional polypeptides or polypeptides having activity other than SEQ ID NO:1.

- The unpredictability of the art and the state of the art: a nucleic acid sequence determines an encoded proteins' structural and functional properties or the identity of a nucleic acid which will hybridize thereto. Predictability of which changes in a polynucleotide can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity and/or utility (in this case sodium-dependent transport of phosphate or the ability to hybridize to a phosphate transport-encoding nucleic acid) requires a knowledge of and guidance with regard to which nucleotides of the encoding sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. In this case, such guidance has not been provided. Furthermore, the positions within an encoding nucleic acid's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide with the desired activity/utility are limited and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given encoded protein to diminish with each further and additional modification, e.g. multiple substitutions. The prior art teaches

that two polypeptides encoded by naturally occurring polynucleotides, while sharing significant sequence homology, may have completely different functions. As a representative example, Seffernick et al. teach that, while a melamine deaminase and atrazine chlorohydrolase differ at only 9 amino acids out of 475 and share 99% nucleic acid identity and greater than 98% amino acid identity, the two enzymes catalyze different reactions, i.e., deamination and dechloronation, and neither enzyme utilizes the other's substrate. Thus, a skilled artisan would recognize the high degree of unpredictability in mutating a protein-encoding polynucleotide with an expectation of maintaining a desired activity and/or utility.

- The amount of experimentation required: While recombinant and mutagenesis techniques and hybridization screening techniques are known, it is not routine in the art to screen for multiple nucleotide substitutions or multiple modifications of naturally and non-naturally occurring nucleic acids, as encompassed by the instant claims. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the instant case, the specification should provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. The specification fails to provide such guidance. Therefore, in view of the broad scope of the claimed nucleic acids and array, the lack of guidance provided by the specification, the unpredictability of the art supported by the state of the art, an undue amount of experimentation would be required for a skilled artisan to make and/or use the claimed nucleic acids and array.

Thus, appellants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including all nucleic acids and the array as described above. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 3-7, 9, 10, 12, and 57 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of US Patent 5,985,604 (hereafter referred to as "Application '604"). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 3-7, 9, 10, 12, and 57 of Application '604 cannot be considered to be patentably distinct over claims 1-8 of the patent when there is a specifically recited embodiment in the patent that would anticipate claims 3-7, 9, 10, 12, and 57 of the instant application. Claims 3-4 of Application '604 are generic to all that is recited in claims 1 and 2 of the patent; claim 5 of Application '604 is generic to all that is recited in claim 3 of the patent; claim 6 of Application '604 is generic to all that is recited in claim 6 of the patent; claim 7 of Application '604 is generic to all that is recited in claim 7 of the patent; claims 9-10 of Application '604 are generic to all that is recited in claim 8 of the patent; and claims 12 and 57 of Application '604 is generic to all that is recited in claims 4-5 of the patent.

(11) Resp nse t Argument

Utility Rejection Under 35 USC § 101

Beginning at the bottom of page 4 of the appeal brief, appellants restate texts of rejections under 35 USC § 101 stated in previous Office actions. Appellants characterize the rejection under 35 USC § 101 as being improper, allegedly because "the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art". Beginning at the bottom of page 5 of the appeal brief, appellants describe their invention as a polynucleotide sequence corresponding to a gene that is expressed in human brain tumor tissue encoding a polypeptide allegedly "demonstrated" in the specification to be a member of the phosphate transporter family having biological functions including regulation of intracellular phosphate levels. Appellants assert the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development and diagnosis of disease, none of which allegedly requires knowledge of the function of the encoded polypeptide. Appellants assert the claimed invention already enjoys significant commercial success. Appellants' argument is not found persuasive.

It is noted that, while the claimed nucleic acid is asserted to have been identified from a sample of human brain tumor tissue, there is no disclosure in the specification that this nucleic acid is expressed only in tumor or brain tumor tissue, nor does the specification disclosure that the claimed nucleic acid has altered expression in tumor or brain tumor tissue as compared to normal tissue. Absent such a disclosure of altered levels or forms of a gene in diseased tissue as compared with the corresponding normal, i.e., healthy, tissue, the gene is not a disease marker or an appropriate target for toxicology testing, drug development, and/or disease diagnosis. It is also noted that appellant's have failed to clearly demonstrate the polypeptide encoded by the claimed polynucleotide to be a member of the phosphate transporter family. Instead, one of ordinary skill in the art clearly recognizes that the disclosed information in the specification merely *predicts or suggests* that the encoded polypeptide has phosphate transporter function based on a shared 48% identity to another phosphate transporter – this is far from a demonstration that the encoded polypeptide belongs to the phosphate transporter family or has phosphate transporter function. In fact, no empirical information regarding the function of the encoded polypeptide has been disclosed in the specification and, as such, appellants have failed to demonstrate

that the encoded polypeptide has *any* biological activity – particularly the ability to transport phosphate. Finally, evidence of commercial success, while sometimes persuasive as secondary evidence of non-obviousness, is immaterial to utility and enablement. Many products have enjoyed commercial success due to fads or clever advertising, wherein the products would not have met the legal standards for utility under 35 USC § 101.

Beginning at the top of page 6 of the appeal brief, appellants discuss the declaration of Dr. Tod Bedilion (the Bedilion Declaration) submitted with appellant's amendment filed December 16, 2002. Appellants characterize the Bedilion Declaration as describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. Appellants assert the Bedilion Declaration demonstrates the examiner's position to be without merit. In particular, appellants state the Bedilion Declaration describes how the claimed polynucleotide can be used in gene expression monitoring systems that were allegedly well known at the time of the invention, and how those applications are useful in developing drugs and monitoring their activity. Appellants quote from the Bedilion Declaration, that states in summary that a cDNA microarray containing a SEQ ID NO:1-encoding polynucleotide would be a more useful tool than a cDNA microarray lacking same in connection with conducting gene expression monitoring studies on proposed or actual drugs for treating disorders associated with increased or decreased phosphate levels for such purposes as evaluating their efficacy and toxicity. Appellants' argument is not found persuasive.

It is noted that Dr. Tod Bedilion is a consultant for Incyte Corporation and thus is a concerned party. Regarding the merit of the examiner's position, *any* polynucleotide can be used in a microarray, just as any polynucleotide can be used for expression of an encoded protein or as a hybridization probe. This asserted utility is *not* specific. The disclosure appears to assert that, because NAPTR (SEQ ID NO:1) has 48% identity to human renal sodium phosphate transport protein (NPT1) and 29% identity to rat brain-specific sodium-dependent inorganic phosphate cotransporter (rBNPI) at the amino acid level, NAPTR functions as a sodium phosphate transport protein. However, sequences sharing identity – even at a relatively high degree do not necessarily share function (see e.g., Seffernick et al.). Furthermore, because NAPTR and NPT1 share identity at the amino acid level does not render the asserted utility specific, since

the specification does not establish a biological or physiological significance of NAPTR, e.g., that NAPTR is expressed in diseased tissues in a form or level that is different from a form or level of the protein expressed in normal tissues. There is no clear indication that NAPTR is a target for drug development, toxicology studies, or disease diagnosis for (quoting from the Bedilion Declaration) "disorders associated with increased or decreased phosphate levels". As such, additional research is required in order to ascertain the function of the encoded protein and/or to identify a potential disease state or states which correlate with altered levels or forms of the claimed polynucleotide.

Beginning at the middle of page 6 of the appeal brief, appellants argue the examiner does not dispute that the claimed polynucleotides can be used as probes in cDNA microarrays and used in gene expression monitoring. Appellants argue the examiner's position is the claimed polynucleotides cannot be useful without precise knowledge of their biological function. Appellants argue the law does not require knowledge of biological function to prove utility and that it is the claimed invention's use(s) that are subject to analysis under the utility requirement. Appellants' argument is not found persuasive.

The examiner acknowledges and agrees with appellants' statement that the claimed polynucleotides can be used as probes in cDNA microarrays and used in gene expression monitoring applications. However, this is *not* a utility that is specific to the claimed nucleic acids. As one of ordinary skill in the art would recognize, any nucleic acid can be used as a probe – this utility is not specific to the claimed nucleic acid and instead applies to the broad class of nucleic acids. It is noted that the examiner disagrees with appellants' assertion that "the Examiner contends that the claimed polynucleotides cannot be useful without precise knowledge of their biological functions". The examiner acknowledges that the utility requirement does not require knowledge of biological function. As previously stated, a claimed polynucleotide can meet the requirements of utility as long as the specification discloses a credible, specific and substantial asserted utility or a well-established utility for the claimed polynucleotide, even though the function of the polynucleotide or encoded polypeptide is not disclosed in the specification. In a previous Office action, the examiner provided the example of Shattuck-Eidens et al. (US Patent 5,693,473) who teach mutant alleles of the *BRCA1* gene that predispose a patient to developing breast and ovarian cancers (abstract). While there is no disclosure of the function of the mutant *BRCA1* genes or

their gene products, the invention nevertheless has utility as being an indicator for susceptibility to developing breast and ovarian cancers. Contrary to this example, the instant specification discloses that the claimed polynucleotides encode a polypeptide that is related by amino acid sequence to other sodium phosphate transport proteins and, based on this association, predicts that the claimed polynucleotide is involved in disorders associated with phosphate transport. Regardless of the function of the claimed polynucleotides or encoded polypeptides, the specification fails to disclose *any* evidence indicating altered forms or expression levels of the claimed polynucleotide in diseased tissue relative to normal tissue and/or that the encoded polypeptide is involved in *any* disease state.

At the bottom of page 6 of the appeal brief, appellants argue that as demonstrated by the Bedilion Declaration, beneficial results can be achieved from the claimed polynucleotide in the absence of any knowledge as to the function of the encoded protein and assert that the use of the claimed polynucleotide in gene expression monitoring applications are in fact independent of their precise biological function. Appellants argue the examiner's assertions that the use of the claimed polynucleotides for gene expression monitoring is not a specific utility without evidence of the function or relation of the claimed polynucleotide to a specific disease state is incorrect. Appellants argue that just because all polynucleotides can be used in toxicology testing does not preclude this utility from being specific, substantial, and credible. Appellants argue all polynucleotides expressed in humans have utility in toxicology testing and that this utility is dependent on the identity of the polynucleotide and not on its function or association to a disease state. Appellants argue the results obtained using an array to detect an expressed polynucleotide is specific to the compound being tested and the detected polynucleotide and therefore, there is no need to link a disease state to the claimed polynucleotide. Appellants argue that, at the very least, an array comprising the claimed polynucleotide can be used as a specific control for toxicology tests. Appellants' arguments are not found persuasive.

If any polynucleotide expressed in a human has utility in toxicology testing, then that polynucleotide has no *specific* utility as all polynucleotides would have such use, regardless of the dependence on the identity of a given polynucleotide and therefore, does not satisfy the utility requirement of 35 USC § 101. In a related example, all polynucleotides have use for protein expression.

The encoded amino acid sequence for any given nucleic acid is specific and dependent upon the identity, i.e., nucleotide sequence, of the encoding nucleic acid. However, as *all* nucleic acids have utility for protein expression, this utility is not specific and therefore does not satisfy the utility requirement of 35 USC § 101. Furthermore, it is noted that the specification provides no guidance to allow a skilled artisan to use data relating to the claimed polynucleotides derived from the results of toxicology testing and what the results would mean. For example, if the claimed polynucleotides were attached to a microarray and used in toxicology testing or gene expression analysis and a result showed that expression was increased when a cell was treated with a particular agent, the specification provides no basis on which a skilled worker would be able to determine whether that result is meaningful. As such, further experimentation would be required to interpret the results of such gene expression analysis. Also, based on the Bedilion Declaration, one of ordinary skill in the art would recognize that knowledge of the function of the protein encoded by the claimed polynucleotide is necessary to be useful for gene expression monitoring in toxicology - even though such use is non-specific. The specification discloses "[t]he discovery of proteins related to human renal sodium phosphate transport protein, and the polynucleotides encoding them, satisfies a need in the art by providing new compositions useful in diagnosis and treatment of diseases associated with increased or decreased phosphate levels" (underline added, page 2, bottom). Also, the Bedilion Declaration states, "a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain any of these polynucleotides, in connection with conducting gene expression monitoring studies on... ...drugs for disorders associated with increased or decreased phosphate levels for such purposes as evaluating their efficacy and toxicity" (emphasis added; Bedilion Declaration, paragraph 15). Therefore, in view of the specification and the Bedilion Declaration, it would appear the biological function of the polypeptide encoded by SEQ ID NO:2 is required for those associated utilities.

I. The Applicable Legal Standard

Beginning at the bottom of page 7 of the appeal brief, appellants cite the following case law that is allegedly relevant to the instant rejection: *Anderson v Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973); *Brenner v Manson*, 383 US 519, 534-35, 148 USPQ 689 (1966); *Juicy Whip Inc. v Orange Bang*

Inc., 51 USPQ2d 1700 (Fed Cir 1999); *Stiftung v Renishaw PLC*, 945 F2d 1173, 1180, 20 USPQ2d 1094 (Fed Cir 1991); *Standard Oil Co. v Montedison, S.p.a.*, 212 USPQ 327 343 (3d Cir 1981); *Cross v Izuka*, 753 F2d 1040, 1048 (Fed Cir 1985); *Nelson v Bowler*, 626 F2d 853, 856, 206 USPQ 881 (CCPA 1980); *In re Cortright*, 165 F3d 1353, 1357, 49 USPQ2d 1464 (Fed Cir 1999); *In re Brana*, 51 F3d 1560, 1566; 34 USPQ2d 1436 (Fed Cir 1995); and *In re Langer*, 503 F2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The essential disagreement between the examiner's position and appellants' position appears to be the interpretation of what constitutes a specific, substantial and credible utility, as will be explained in detail below.

II. Toxicology testing, drug discovery, and disease diagnosis are allegedly sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph.

Appellants argue the claimed invention meets all necessary requirements for establishing a credible utility under the law as appellants allege there are "well-established" uses for the claimed invention known to persons of ordinary skill in the art and there are allegedly specific practical and beneficial uses disclosed in the specification for the claimed invention. Appellants argue these uses are explained in the Bedilion Declaration and that objective evidence, allegedly not considered by the Office, further corroborates the credibility of the asserted utilities. Appellants' arguments are not found persuasive.

The claimed invention has no well-established use and there is no specific, substantial and credible use for the claimed invention, even after full consideration of the "objective evidence" as provided in the specification. Each of these arguments will be described in more detail below. Also, contrary to appellants' assertion, it is noted that the examiner has fully considered all evidence as provided by appellant in evaluating the claims for utility under 35 USC § 101.

A. The use of the claimed polynucleotides for toxicology testing, drug discovery, and disease diagnosis are allegedly practical uses that confer specific benefits to the public.

Beginning at the bottom of page 9 of the appeal brief, appellants argue the claimed invention has real-world utility as allegedly being useful for toxicology testing, drug discovery, and disease diagnosis

through gene expression profiling. Appellants argue these uses are explained in the Bedilion Declaration, the substance of which appellants assert is not rebutted by the Office action. Appellants argue there is no dispute that the claimed invention is a useful tool in cDNA microarrays used to perform gene expression analysis. Appellants assert that these uses are sufficient to establish utility for the claimed polynucleotide. Appellants' arguments are not found persuasive.

Regarding the substance of the Bedilion declaration, the examiner agrees with the Bedilion Declaration to the extent that *any* polynucleotide, including the claimed polynucleotides, can be included as part of a cDNA microarray, however, this does not confer patentable utility on the claimed polynucleotides as this utility is considered a general use and not a utility that is specific and substantial. MPEP 2107.01 states, "A 'specific utility' is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention". Polynucleotides have a variety of general uses, such as for hybridization, protein expression, and as a component of a cDNA microarray – these uses are applicable to *any* polynucleotide and are not specific to the claimed polynucleotide. Also, the claimed polynucleotide has no substantial utility. MPEP 2107.01 states, "Utilities that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities". Since the specification does not disclose sufficiently convincing evidence of the function of the polypeptide encoded by SEQ ID NO:2 and/or a correlation between any *particular* disease or disorder and an altered level or form of the claimed polynucleotide and/or or guidance to allow a skilled artisan to use data relating to the claimed polynucleotides derived from the results of toxicology testing and what the results would mean, the results of gene expression monitoring assays using a cDNA microarray comprising the claimed polynucleotide would be meaningless without further research. MPEP 2107.01 provides an example of a substantial utility as follows: "An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a 'real world' context of use". As stated above, the specification does not disclose a correlation between any *particular* disease or disorder and an altered level or form of the claimed polynucleotide. MPEP 2107.01 also provides examples of utilities that are *not* substantial, including: "A method of assaying for or identifying a material that itself has no specific and/or substantial utility". The

claimed polynucleotide has no specific and/or substantial utility, therefore, the use of a cDNA microarray for measuring levels of the claimed polynucleotide is not substantial.

Beginning at page 13 of Paper No. 7, appellants refer to the Bedilion declaration as explaining the many reasons why a person skilled in the art reading the instant application would have understood this application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, such as a probe for expression of the polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. Specifically, appellants quote from the Bedilion declaration that a person skilled in the art would have been able to use the claimed polynucleotide in gene expression monitoring to develop new drugs for the treatment of disorders associated with increased or decreased phosphate levels. Appellants' arguments are not found persuasive.

The instant specification does not substantiate a link between the claimed polynucleotides and any *specific* disorder associated with increased or decreased phosphate levels. The specification merely discloses that the claimed polynucleotide encodes a polypeptide that is structurally related to a sodium-dependent phosphate transporter (see for example page 22 of the instant specification). MPEP 2107.01 states, "Utilities that require or constitute carrying our further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities". Since the specification does not disclose convincing evidence of the function of the polypeptide of SEQ ID NO:2 and/or a correlation between any *particular* disease or disorder and an altered level or form of the claimed polynucleotide, the results of gene expression monitoring assays using a cDNA microarray comprising the claimed polynucleotide would be meaningless without further research. MPEP 2107.01 provides an example of a substantial utility as follows: "An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a 'real world' context of use". As stated above, the specification does not disclose a correlation between any *particular* disease or disorder and an altered level or form of the claimed polynucleotide. The specification does not disclose any results that would enable a skilled artisan to draw any conclusions regarding a disorder, namely, that the expression of the claimed polynucleotide is expressed at an altered level or form as compared to the

corresponding normal tissue. Many genes expressed in diseased tissues have no connection to the disease itself and are not targets for drug development or toxicology.

Beginning at the last paragraph of page 10 of the appeal brief, appellants refer to the opinion of Dr. Bedilion who states that a person skilled in the art at the time of the invention would have concluded that a cDNA microarray containing the claimed polynucleotide would be a more useful tool than a microarray lacking the claimed polynucleotide in connection with conducting gene expression monitoring studies on proposed or actual drugs for disorders associated with increased or decreased phosphate levels for purposes of evaluating their efficacy and toxicity. Appellants' arguments are not found persuasive.

As previously stated, the instant specification has not established the claimed polynucleotides as being expressed at an altered level or form in a diseased tissue as compared with the corresponding normal tissue or guidance to allow a skilled artisan to use data relating to the claimed polynucleotides derived from the results of gene expression analysis and what the results would mean. As appellants have provided no evidence that the claimed polynucleotides are involved in disorders associated with altered phosphate levels, if, for example, the claimed polynucleotide was a component of a microarray and a test compound resulted in decreased expression of the claimed polynucleotide, further experimentation would be required to interpret the hybridization results. Disclosure of the claimed polynucleotide as being expressed at an increased level in a specific disorder associated with altered levels of phosphate as compared with the corresponding normal tissue would provide a skilled artisan with an indication that a given test compound that decreased expression of the polynucleotide is a potential candidate drug. However, such disclosure has not been provided and the claimed polynucleotides may very well be expressed at equivalent levels in normal tissues. In the absence of any disclosed relationship between the claimed polynucleotide or the encoded protein and any *specific* disease or disorder, any information obtained from an expression profile would only serve as the basis for further experimentation on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*

v. Manson, 148 USPQ at 696. As such, the disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. § 101.

Beginning at the first full paragraph of page 11 of the appeal brief, appellants discuss the Bedilion Declaration's detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations. Appellants point to Dr. Bedilion's pages of text and numerous subparts explaining the importance of this technology. Appellants point to Dr. Bedilion's explanation that those skilled in the art at the time of the invention without any doubt would have appreciated the criticality of toxicity testing. Appellants' arguments are not found persuasive.

While there is no doubt that cDNA microarray technology is an extremely valuable technique in gene expression monitoring, toxicology testing, and drug efficacy testing, the claims are not drawn to this technique. Instead, the claims are directed to polynucleotides that have not been disclosed as being associated with any particular disease or condition and the specification provides no guidance as to how to interpret data obtained from gene expression analysis. As stated above, *any* polynucleotide can be a component of a microarray. Thus, this asserted utility is not specific. Determining the relationship between the claimed polynucleotides and any *specific* disease or disorder or interpreting the results of gene expression monitoring based on the teachings of the instant specification would require significant further research. Therefore, this asserted utility is also not substantial.

At the bottom of page 11 of the appeal brief, appellants assert the Bedilion Declaration establishes that persons skilled in the art, guided by the instant specification, at the time of the invention would have wanted their cDNA microarrays to comprise the claimed polynucleotides, because a microarray comprising the claimed polynucleotide would allegedly provide more useful results in the kind of gene expression monitoring studies than microarrays lacking the claimed polynucleotide. Appellants argue that Dr. Bedilion's opinion by itself provides more than sufficient reason to compel the conclusion to persons skilled in the art that the claimed polynucleotides have a substantial, specific, and credible utility. Appellants' arguments are not found persuasive.

The specification provides no correlation or nexus between the claimed polynucleotide and any *specific* disease state or disorder or guidance as to how to interpret data obtained from gene expression

analysis. Incorporating the claimed polynucleotide into a microarray would not make the microarray any more valuable than adding any other human polynucleotide. The asserted utility is not specific to the claimed polynucleotide.

At the top of page 12 of the appeal brief, appellants argue the examiner does not address the "fact" that the claimed polynucleotide can be used as highly specific probes to measure both the existence and amount of complementary mRNA sequences known to be expression products of the claimed polynucleotides. Appellants conclude that the claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine. Appellants' arguments are not found persuasive.

As stated above, *any* polynucleotide is a highly specific probe for itself or its complement, or any mRNA that can be transcribed from it. Such can be said for *any* polynucleotide. As previously stated, MPEP 2107.01 provides an example of a utility that is *not* substantial as follows: "A method of assaying for or identifying a material that itself has no specific and/or substantial utility". The claimed polynucleotide has no specific and/or substantial utility, therefore, the use of a cDNA microarray comprising the claimed polynucleotide for measuring levels of itself is *not* substantial.

At the second full paragraph of page 12 of the appeal brief, appellants argue that, given that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. Appellants cite case law as allegedly relevant to the patentable utility of research tools. Appellants' arguments are not found persuasive.

It is true that a scale, gas chromatograph, screening assays, and nucleotide sequencing techniques have utility as research tools. However, such tools present a result that requires no further experimentation for interpretation, e.g., a scale provides the weight of an object and requires no further experimentation for interpretation of the result. In the instant case, a more representative analogy to the claimed polynucleotides and array would be that of a scale without an identifiable unit of measure - one could place an object on the scale, however, further experimentation would be required to interpret the result and determine the weight of the object. Similarly, as appellants have provided no information

regarding altered expression of the claimed polynucleotide or guidance for interpreting the results of gene expression analysis, additional experimentation would be required to interpret a result of altered polynucleotide expression obtained using a microarray comprising the claimed polynucleotides. As stated above, the specification does not disclose a correlation between any *particular* disease or disorder and an altered level or form of the claimed polynucleotide or provide guidance for interpreting the results of gene expression analysis. Therefore, the assertion that the claimed polynucleotide has patentable utility as a probe in, or a member of, a microarray is not substantial.

Beginning at the third full paragraph of page 12 of the appeal brief, appellants argue there can be no reasonable dispute that persons skilled in the art have numerous uses for information about relative gene expression including understanding the effects of a potential drug for treating disorders associated with increased or decreased phosphate levels. Appellants argue that, since the specification discloses the claimed polynucleotide to be expressed in brain tumor cells and expresses a protein that is allegedly a member of a class of proteins that regulate intracellular phosphate levels, there can be no dispute that an ordinarily skilled artisan could put the claimed invention to such use, i.e., derive more information about relative gene expression than without it. Appellants' arguments are not found persuasive.

While the specification does indicate that the nucleic acid of SEQ ID NO:2 is expressed in brain tumor tissues (see page 35 of the instant specification), there is no indication that expression of SEQ ID NO:2 is specific for brain tumor tissues as opposed to ubiquitous expression or expression in other normal or tumorous tissues. Nor is there indication that this nucleic acid has altered expression in tumor or brain tumor tissue as compared to normal tissue. The specification does *not* disclose the claimed polynucleotide as being expressed at an altered level or form in any particular disease or disorder as compared to the corresponding normal tissue(s). Other than functional assignment of the polypeptide of SEQ ID NO:1 based solely on the amino acid sequence characteristics, there is no further indication that the polypeptide encoded by SEQ ID NO:2 is involved in phosphate transport. Furthermore, even if it can be assumed *arguendo* that the claimed polynucleotides play a role in a disorder associated with increased or decreased phosphate levels, determining which disorder(s) is/are involved and if and how the claimed polynucleotides are altered during the disorder requires significant further research. Absent

such a disclosure of altered levels or forms of a gene in diseased tissue as compared with the corresponding normal, i.e., healthy, tissue, or guidance as to how one of ordinary skill can interpret data obtained from a gene expression analysis using the claimed polynucleotides, further experimentation is necessary to use the claimed polynucleotide to derive information about a potential drug candidate.

Beginning at the first full paragraph at page 13 of the appeal brief, appellants refer to Dr. Bedilion's opinionated discussion of Brown et al. (US Patent 5,807,522, cited by appellants). Dr. Bedilion characterizes the patent as providing evidence that microarrays can be used in numerous genetic applications, including monitoring of gene expression in different tissue types, disease states, in response to drugs, and in response to potential toxins. Appellants' arguments are not found persuasive.

The claims of the Brown et al. patent are drawn to methods of forming microarrays (see, for example, claim 1 of Brown et al.). Methods of forming a microarray have patentable utility. However, in the instant case, a microarray comprising the claimed polynucleotide does not have patentable utility as stated in detail above.

Beginning at the middle of page 13 of the appeal brief, appellants cite the references of Rockett et al. (*Xenobiotica* 29:655) and Lashkari et al. as allegedly describing the use and importance of gene expression technology with respect to drug screening and toxicology testing. Appellants' arguments are not found persuasive.

Appellants' arguments and alleged supporting evidence merely indicate that microarray technology is important and useful to the scientific community. These publications are unrelated to the claimed polynucleotide and fail to demonstrate the claimed invention has *any* patentable utility. The use of the claimed and functionally uncharacterized polynucleotides in such studies would provide no more information than the use of any other uncharacterized polynucleotide. The asserted utility for the claimed polynucleotide is not specific to the claimed polynucleotide as stated above. Furthermore, due to the lack of disclosure of a correlation between the claimed polynucleotides and a particular disorder or guidance for interpreting the data obtained from gene expression analysis, the asserted utility is also not substantial, as discussed in detail above.

In the last paragraph at page 14 of the appeal brief, appellants argue the claimed polynucleotides are not the object of research and are instead a research tool used to assess the toxicity of drug candidates which are specifically targeted to other polynucleotides. Appellants argue it is the other polynucleotides and drug candidates that are the object of the research. Appellants' arguments are not found persuasive.

In response to appellants' argument, it is noted that a research tool such as a scale has an unquestionable utility – one of ordinary skill in the art would know how to use the scale as a research tool without further experimentation. This is not true of the instant invention. The specification simply provides no guidance regarding what specific information derived from a microarray comprising the claimed polynucleotides would mean. As such, it appears that appellants' position is that the claimed polynucleotides are useful as a research tool because those of skill in the art could experiment to determine for themselves the meaning of any observed experimental results. This does not provide a "specific benefit in currently available form." Here, the appellants claim a product asserted to be useful in a method of generating gene-expression data, but the specification does NOT disclose how to interpret those data. As such, the product claims here lack utility, based on their asserted use as research tools, because the specification does not disclose how to use the SEQ ID NO:2-specific gene expression data generated by expression analysis.

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is allegedly "well-established".

At the top of page 15 of the appeal brief, appellants argue the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of disease and that these uses are "well-established". Appellants cite the references of Rockett et al. (*Xenobiotica* 29:655), Nuwaysir et al., Steiner et al., Rockett et al. (*Environ Health Perspectives* 107:681), and an email from Dr. Cynthia Afshari to an Incyte employee, and examples (as set forth at the bottom of page 16 of the appeal brief) that allegedly support appellants' assertions. Appellants argue that, because the examiner has allegedly failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug

development, and disease diagnosis, the rejections should be withdrawn. Appellants' arguments are not found persuasive.

Each of these uses (toxicology testing, drug development, and disease diagnosis) will be addressed individually, because the facts and issues directed to each use are distinct and separable. First, appellants argue that toxicology testing is a well-established utility and concludes that the claimed polynucleotides could be used in this manner and that the claimed invention therefore possesses patentable utility. However, for a utility to be "well-established" it must be specific, substantial and credible. In this case, as acknowledged by appellant at page 7, lines 7-8 of the appeal brief, "all polynucleotides expressed in humans have utility in toxicology testing" and thus, just because a polynucleotide can be used for toxicology testing, this does not by default provide patentable utility to any expressed polynucleotide. Furthermore, the specification fails to disclose the methods and information necessary for a skilled artisan to use the claimed polynucleotide for toxicology testing. Therefore, this is a utility that would apply to virtually every member of a general class of materials, such as any collection of polynucleotides. Thus, such a utility is *not* specific and does *not* constitute a "well-established" utility. Moreover, use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gleaned from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Again, this is a utility that would apply to virtually every member of a general class of materials, such as any collection of polynucleotides. Even assuming *arguendo* that the expression of appellants' claimed polynucleotide was affected by a test compound in an array for drug screening, the specification does not disclose any guidance for interpretation of the result, and none is known in the art. Given this consideration, the individually claimed polynucleotides have no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information generated using this nucleic acid may have.

With regard to drug discovery and development, appellants mention gene expression profiling as one use of the claimed polynucleotides. Appellants refer to recent developments as providing evidence that the benefits of this information are already beginning to manifest themselves. However, appellants

are incorrect in asserting that the efficacy (ability to produce a desired effect) of a compound could be evaluated from the result of a transcript image because there is no way to assess the meaning of any individual "hit" obtained from this procedure. The first requirement is that one must know the biological significance of the polynucleotide(s) which is/are being evaluated. Without this information, the results of the transcript image are useless because one would not inherently recognize how to interpret the result of increased or decreased polynucleotide expression or even what significance could be attributed to such changes in expression profiles. As such information has not been provided in the specification, further experimentation is required to identify a "real world" use for the claimed polynucleotide.

With regard to diagnosis of disease, in order for a polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in tissue that is derived from brain tumor cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed polynucleotide and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many polynucleotides are expressed at equal levels and in identical forms in both normal *and* diseased tissues. Therefore, one necessarily needs to know, e.g., that the claimed polynucleotide is either present only in brain tumor tissue to the exclusion of normal tissue or is expressed in higher levels in brain tumor tissue compared to normal tissue. Evidence of a differential expression *might* serve as a basis for use of the claimed polynucleotides as a diagnostic for disease(s). However, in the absence of any disclosed relationship between the claimed polynucleotides or encoded proteins and any disease or disorder and the lack of any correlation between the claimed polynucleotides or the encoded proteins with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. Also, because any potential diagnostic utility is not yet known and has not

yet been disclosed, the utility is not substantial because it is not currently available in practical form and would thus require further research for its implementation. Thus, the disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. § 101.

C. The similarity of the polypeptide encoded by the claimed invention to another polypeptide of undisputed utility is asserted to demonstrate utility.

Beginning at the top of page 17 of the appeal brief, appellants argue that the utility of the claimed polynucleotides can be imputed based on the relationship between NAPTR and another polypeptide of unquestioned utility, human renal sodium phosphate transport protein (NPT1). Appellants argue that NAPTR shares more than 48% sequence identity over 401 amino acid residues with NPT1, that NAPTR, NPT1, and rat brain-specific sodium-dependent inorganic phosphate cotransporter all share a *potential* N-glycosylation site, and have rather similar hydrophobicity plots. Appellants conclude that these results are sufficient to demonstrate a reasonable probability that the utility of NPT1 can be imputed to the claimed polynucleotide. Appellants cite Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078; hereafter referred to as "Brenner et al. (1998)") as evidence that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Appellants argue the Office must accept appellants' demonstration that the homology between NAPTR and NPT1 demonstrates utility by a reasonable probability unless evidence or sound scientific reasoning is presented such that a person of ordinary skill in the art would doubt utility. Appellants argue that none of the references cited by the examiner (van de Loo et al., Seffernick et al., Broun et al., Bork, Scott et al., Vrljic et al., Tenenhouse et al., Murzin et al., and Brenner (1999) suggests that functional homology cannot be inferred by a reasonable probability in this case. Appellants argue that none of the cited references contradicts the basic "rule" of Brenner et al. (1998) that two unrelated polypeptides sharing more than 40% sequence homology over 70 amino acid residues yields a high probability of functional homology as well or Bork's findings of a 70% accuracy rate for bioinformatics-based predictions in general and a 90% accuracy rate for the prediction of functional homology. Appellants argue the cited references at best demonstrate that it is difficult to make predictions about function with certainty and not reasonable probability. Appellants' arguments are not found persuasive.

As far as the asserted "unquestioned" utility of NPT1, the instant application is not drawn to nucleic acids encoding NPT1, and, to that extent, the utility of NPT1 is not at issue. Even assuming *arguendo* that the utility of NPT1 is at issue, the specification provides no asserted utility for NPT1 and there is no evidence of record of a well-established utility for NPT1. It is further noted that the issue at hand is the utility of the claimed polynucleotides and not the utility of the encoded polypeptide. As the specification has *not* established with a reasonable probability that the polypeptide of SEQ ID NO:1 shares the same function as NPT1 or belongs to the class of phosphate cotransporters, the utility of NPT1 or phosphate transport proteins as a class is not at issue. While the polypeptide encoded by SEQ ID NO:2 may share more than 48% sequence identity over 401 amino acid residues with NPT1, this is no indication that the polypeptide encoded by SEQ ID NO:2 shares the same function as NPT1. One of ordinary skill in the art would recognize that, while sequence identity between two polypeptides can be used to *predict, i.e., suggest,* function, empirical analysis is the only method of confirming a protein's function with a reasonable probability.

It is noted that appellants argue at great length throughout the appeal brief that sequence comparison methods can be used to prove function in the absence of any functional characterization. The examiner fully disagrees. However, in order to be fully responsive, the examiner has responded to all of appellants' lengthy arguments addressing functional assignment based on sequence comparison methods.

The reference of Brenner et al. (1998) merely indicates that sequence comparison algorithms can be used to identify distinct evolutionary relationships and the reference of Bork indicates that sequence comparisons can be used to *predict or suggest* the function of an uncharacterized protein. These references fail to demonstrate the claimed invention has *any* patentable utility. Appellants improperly attempt to apply the teachings of Brenner et al. (1998) and Bork (*Genome Res* 10:398-400) to the asserted 48% identity between NAPTR (SEQ ID NO:1) and NPT1. The study of Brenner et al. (1998) has been conducted to identify distant evolutionary homology using sequence comparison algorithms. Nowhere does Brenner et al. state their results can be extrapolated for use in predicting functional homology. Furthermore, Brenner et al. (1998) clearly state that their comparisons "have been assessed

using proteins whose relationships are known reliably from their structures and functions, as described in the SCOP database" (page 6073, abstract). The art recognizes the proteins within the SCOP database have been *fully characterized*, meaning their functions have been characterized by empirical laboratory experiments and their three dimensional structures have been generated (see for example Murzin et al. Brenner et al. (1998) are silent as to the use of their results to the functional assignment of an uncharacterized protein. In this case, appellants quote a portion of Brenner et al. (1998) out of context and attempt to use these teachings to inappropriately support their argument. In fact, the results of Brenner et al. (1998) are applicable ONLY for identifying evolutionary homology – not functional homology. Even assuming *arguendo* that the results of Brenner et al. (1998) could be applied to functional annotation – which they cannot – it is unclear as to whether these results would be applicable to an uncharacterized protein as Brenner et al. (1998) teach their results are specific for the database used in the study by stating, "30% identity is a reliable threshold for [the PDB90D-B database]" and that, "40% is a reasonable threshold, for a database of this particular size and composition". In the instant case, neither the specification nor the prior art provides a functional characterization of NAPTR and there is no evidence of record that NAPTR has phosphate transporter function and *it is just as likely that NAPTR has no function at all*. Brenner et al. (1998) fails to demonstrate the claimed invention has *any* patentable utility.

Regarding the reference of Bork, it is noted that Bork clearly states that gene annotation has a "considerable" error rate (page 399, middle column) and provide a footnote to Table 1, which states that the evidence provided is a crude estimate and that "numbers in Table 1 are often overestimates because the test sets used are usually not representative of all sequences". Furthermore, Bork fails to demonstrate the claimed invention has *any* patentable utility.

Thus, one of ordinary skill in the art would recognize the fallacy of attempting to relate the teachings of Brenner et al. (1998) and Bork (*Genome Res* 10:398-400) to a functional assignment of NAPTR based on a relatively low sequence homology to NPT1.

Even assuming *arguendo* that the results of Brenner et al. (1998) and Bork (*Genome Res* 10:398-400) are relevant in this case – which they are not – Brenner et al. (1998) and Bork (*Genome Res*

10:398-400) are silent as to the determination of whether a polypeptide actually has *any* biological activity. In this regard, empirical characterization is required to ascertain the presence of a detectable biological activity. Provided the disclosed teachings of the instant specification, there is simply no way of knowing the biological function – if any – of NAPTR without empirical evidence. The function of NAPTR has been assigned solely on the basis of a relatively low sequence identity to NPT1. Other than structural features, the specification provides no further characterization of NAPTR and it is just as likely that the polypeptide of NAPTR has NO biological activity, i.e., it is a non-functional polypeptide. Other than solely structural features, there is no evidence of record to suggest that NAPTR has phosphate transporter activity and the cited references make clear that such functional assignment of a polypeptide based solely on structural features cannot be made with certainty. It is noted that appellants assert "[t]he claimed polynucleotide encodes a polypeptide demonstrated... ...to be a member of the phosphate transporter family, whose biological functions include regulation of intracellular phosphate levels" (page 5, bottom of the appeal brief). However, appellants have yet to demonstrate NAPTR has *any* biological activity – it is just as likely that the encoded polypeptide is without function. Brenner has expressed his views on functional assignment of a protein based solely on sequence analysis in a manuscript titled "Errors in Genome Annotation" (*Trends Genetics* 15:132-133; hereafter referred to as "Brenner (1999)"). In this reference, Brenner (1999) teaches that laboratory experiments are required to verify a protein's function (page 132, left column, second paragraph) and describes the errors that are inherent in predicting function based on sequence identity. For example, Brenner (1999) states, "[w]ithout laboratory experiments... ...it is impossible to know for certain [whether the function assigned to a protein by annotation is correct]" (page 132, left column, second paragraph). Thus, based on the teachings of Brenner (1999), one of ordinary skill in the art recognizes that such generalized teachings of Brenner et al. (1998) cannot be applied in a wholesale fashion as asserted by appellants. Instead, the examiner has cited the references of van de Loo et al., Seffernick et al., Broun et al., and Scott et al. as evidence showing that homology between protein sequences – even at a particularly high level – is not indicative of identical function. The reference of Scott et al. is most relevant to the instant case. Scott et al. teach a polypeptide that has 45% sequence identity (it is noted that NAPTR similarly shares 48% identity with

NPT1) with a human sulfate transporter and that, based on structural homology has been proposed to function as a sulfate transporter (page 440, left column, abstract). However, an empirical analysis of the protein revealed that the protein is not a sulfate transporter and is actually a chloride-iodide transport protein (page 441, left column, third full paragraph). Scott et al. conclude that, "[t]hese results underscore the importance of confirming the function of newly identified gene products even when database searches reveal significant homology to proteins of known function" (page 441, left column, third full paragraph). Thus, a skilled artisan would recognize that the function of a polypeptide cannot be assigned based on solely on sequence identity, and would conclude that the specification has *not* established with a reasonable probability that the polypeptide of SEQ ID NO:1 shares the same function as NPT1 or belongs to the class of phosphate cotransporters.

Also, while NAPTR, NPT1, and rat brain-specific sodium-dependent inorganic phosphate cotransporter may all share a *potential* N-glycosylation site, an ordinarily skilled artisan would recognize that nearly all full-length proteins exhibit a *potential* N-glycosylation site and therefore, would not be a factor in a determination of whether NAPTR and NPT1 share the same function.

Furthermore, while NAPTR, NPT1, and rat brain-specific sodium-dependent inorganic phosphate cotransporter may have rather similar hydrophobicity plots, such plots have been shown to be similar even among proteins with relatively low sequence homology that exhibit different functions. For example, Vrljic et al. analyze the hydrophobicities of three proteins that function in the transport of different molecules (page 329, Figure 2) revealing strikingly similar hydrophobicity plots. Thus, based on the cited references, an ordinarily skilled artisan would recognize that a protein's function *cannot* be assigned based on structural identity alone. Empirical evidence is required to verify the function of a polypeptide, which, in this case has not been provided. Thus, one of ordinary skill in the art would not recognize with a reasonable probability that the polypeptide of SEQ ID NO:1 encoded by the polynucleotide of SEQ ID NO:2 has function similar to NPT1.

In this case, appellants clearly attempt to use the references of Brenner et al. (1998) and Bork to assert that function can be *proven* rather than *predicted* based on sequence homology. There is no evidence of record to suggest that one can prove function based on sequence homology and the

references cited by the examiner show that only by empirical characterization can one determine the function of a polypeptide. Beyond *suggesting* the function of NAPTR based on sequence homology, the specification fails to demonstrate NAPTR has *any* biological activity, or more specifically, phosphate transporter activity, and further experimentation is required to verify its function. Furthermore, without verifying the function of NAPTR, there is no basis on which a skilled worker would be able to determine whether a result obtained by gene expression analysis in connection with developing new drugs for treatment of disorders associated with increased or decreased phosphate levels (as explained in the Bedilion Declaration and page 10, bottom of the appeal brief) is meaningful.

Thus, appellants' argument that none of the previously cited references contradicts the basic "rule" of Brenner et al. (1998) is without merit as the teachings of Brenner et al. (1998) are not applicable to the instant case for those reasons stated above. While a skilled artisan would recognize that the function of a polypeptide can be *predicted or suggested* based on sequence identity, function cannot be demonstrated based solely on amino acid sequence, and would conclude that the specification has *not* established with a reasonable probability that the polypeptide of SEQ ID NO:1 has *any* biological activity or, more specifically, shares the same function as NPT1 or belongs to the class of phosphate cotransporters, particularly in view of the teachings of Scott et al.

D. Objective evidence allegedly corroborates the utilities of the claimed invention.

Beginning at the bottom of page 18 of the appeal brief, appellants argue that a "real-world" utility exists if actual use or commercial success can be shown. Citing case law, appellants state that such a showing of actual use or commercial success is conclusive proof of utility. Appellants argue that a vibrant market has developed for databases containing all expressed genes, including those of Incyte, the real party at interest. Appellants state Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven valuable, and that the databases including the claimed polynucleotide would be even more valuable. Appellants argue that customers can purchase the claimed polynucleotides from Incyte, saving the customer time and expense. Appellants' arguments are not found persuasive.

The case law indicates that a rejection under 35 U.S.C. § 101 *for lack of operability* can be overcome by a showing of actual use or commercial success. The instant issue is whether or not the asserted utilities meet the three-pronged test for credibility, specificity, and substantiality. Such is not necessarily addressed by a showing of commercial success or actual use. As argued previously, many products that lack patentable utility enjoy commercial success, are used, and are considered valuable and appellants' asserted utilities are neither substantial or specific. Furthermore, while appellants present evidence showing that the database is commercially valuable, there is no evidence to suggest that the database is any more or less valuable with the inclusion of the *claimed* polynucleotide or that customers would desire to purchase the claimed polynucleotide.

III. The patent examiner's rejections are allegedly without merit.

Beginning at the bottom of page 19 of the appeal brief, appellants argue that, rather than responding to the evidence allegedly demonstrating utility, the examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the clamed polynucleotides are not "specific and substantial asserted" utilities. Appellants argue the examiner is incorrect both as a matter of law and as a matter of fact. Appellants' arguments are not found persuasive.

The claimed invention has no well-established use and there is no specific or substantial use for the claimed invention, even after FULL consideration of the "evidence" as provided in the specification. Appellants' arguments will be addressed in detail below.

A. The precise biological role or function of an expressed polynucleotide is alleged as being not required to demonstrate utility.

Appellants characterize the examiner's rejection as being based on the grounds that, without information as to the precise biological role of the claimed invention, the claimed invention lacks specific patentable utility. Appellants argue that, according to the examiner, it is not enough that a person skilled in the art could use and would want to use the claimed invention either by itself or in a microarray, but that appellants are also required to provide a specific and substantial interpretation of the results generated in a given expression analysis. Appellants argue that specific and substantial interpretations regarding biological function may be required by technical journals, but are not necessary for patents. Appellants

state the relevant question is not how or why the invention works, but whether the invention provides an identifiable benefit. Appellants argue that the present invention meets this test. Appellants argue that the threshold for patentable utility is low and that only throwaway utilities are insufficient, and that knowledge of biological function is not required. Appellants' arguments are not found persuasive.

It is noted that appellants' arguments have mischaracterized the examiner's position. The examiner has fully considered appellants' "evidence" allegedly demonstrating utility and, in accordance with 35 USC § 101 has determined the claimed invention to lack patentable utility. Furthermore, the rejection never states that the precise biological role of a polynucleotide is required for it to possess patentable utility (see the example of Shattuck-Eidens et al. in US Patent 5,693,473 as described above). However, the specification fails to disclose sufficient information such that one of skill in the art can use the claimed polynucleotide as a disease marker or for toxicology testing, drug discovery, or disease diagnosis and as such, there is no specific and substantial asserted utility. For example, if the claimed polynucleotide were used in a microarray for toxicology testing and if a compound caused the claimed polynucleotide to be expressed at a decreased level as demonstrated by the data generated using the microarray, what information does this provide, other than to initiate further experimentation? In view of the specification, a skilled artisan would recognize that the determination of whether a compound is potentially therapeutic or deleterious requires significant further research, and thus the asserted utility is not substantial. Also, *any* expressed polynucleotide *can* be used in a microarray – just as any polynucleotide can be used for protein expression and thus the asserted utility is also not specific.

B. Membership in a class of useful products can allegedly be proof of utility.

Beginning at the top of page 21 of the appeal brief, appellants assert the examiner has refused to impute the utility of the members of the phosphate transporter family to NAPTR. Appellants argue the examiner takes the position that utility of the claimed polynucleotides cannot be imputed unless appellants identify which particular biological function within the class of phosphate transporters is possessed by NAPTR. Appellants argue the examiner would require that all phosphate transporters possess a "common" utility in order to demonstrate utility by membership in a class of phosphate transporters. Appellants state the case law requires only that the class not contain a substantial number

of useless members. Appellants argue the examiner has treated NAPTR as if it was in a general class of all polynucleotides, rather than the phosphate transporter class. Appellants argue the examiner has not presented any evidence that the phosphate transporter class of proteins has any, let alone a substantial number, of useless members.

As described above, appellants *predict* NAPTR shares function with NPT1 and belongs to the class of phosphate transport proteins based on solely structural characteristics. There is no evidence of record to demonstrate the claimed polynucleotide encodes a polypeptide whose biological functions include regulation of intracellular phosphate levels as asserted by appellant (see, e.g., page 5, bottom of the appeal brief). Appellants provide NO functional characterization of NAPTR and it is just as likely that the polypeptide has no biological activity or a completely unrelated biological activity. As stated above, the cited references support the examiner's argument that one cannot demonstrate function to a high degree of certainty in assigning protein function based solely on structural characteristics. Thus, one of ordinary skill in the art would conclude that the specification has *not* established with a reasonable probability that the polypeptide of SEQ ID NO:1 shares the same function as NPT1 or belongs to the class of phosphate cotransporters, particularly in view of the teachings of Scott et al. who teach, "the importance of confirming the function of newly identified gene products even when database searches reveal significant homology to proteins of known function" (page 441, left column, third full paragraph) and Brenner (1999) who teaches, "[w]ithout laboratory experiments... ...it is impossible to know for certain [whether the function assigned to a protein by annotation is correct]" (page 132, left column, second paragraph). Thus, the class of phosphate transport proteins cannot be used to predict utility for a new polypeptide that is included in the class based solely on sequence identity to another member of the class. Furthermore, there is no evidence of record to support an asserted specific and substantial utility or a well-established utility for the *entire* class of phosphate transporters.

At the middle of page 22 of the appeal brief, appellants argue that even if the examiner's common utility criterion were correct, the phosphate transport family would meet it. Appellants argue the phosphate transporter family is known to regulate intracellular phosphate levels, and the person of ordinary skill in the art need not know anything more about the claimed invention in order to be able to use it and the

Office action presents no evidence to the contrary. Appellants argue the examiner concludes that a skilled artisan would need to know whether any given phosphate transporter carries out a particular role in intracellular phosphate level regulation and that NAPTR is useful only for further study of NAPTR. Appellants argue that knowledge that NAPTR is a phosphate transporter is sufficient to make it useful for diagnosis and treatment of disorders associated with altered phosphate levels. Appellants argue NAPTR has been shown to be expressed in human brain tumor tissues. Appellants conclude that these facts must be accepted as true in the absence of evidence or sound scientific reasoning to the contrary. Appellants' arguments are not found persuasive.

As stated above, the specification fails to provide convincing evidence that NAPTR is a phosphate transporter and there is no evidence of record of a substantial and specific and/or a well-established utility for the *entire* class of phosphate transport proteins. As previously stated, the specification provides no guidance for diagnosing or treating disorders associated with altered phosphate levels. Thus, further experimentation would be required to determine if the polypeptide encoded by SEQ ID NO:2 indeed functions as a phosphate transporter and, if so, what - if any - connection can be made to a specific disorder. While NAPTR may be expressed in brain tumor tissues, the specification has provided no evidence that NAPTR is *not* expressed in other tissues or at a level or form that is different in brain tumor tissues from that of normal tissues such that a skilled artisan could use the polynucleotide, e.g., as a disease marker. As such, significant further research would be is necessary for the skilled artisan to use the claimed polynucleotides in a real world context, and thus the asserted utility is not substantial.

C. The uses of the claimed polynucleotides in toxicology testing, drug discovery, and disease diagnosis are allegedly practical uses beyond mere study of the invention itself.

At the top of page 23 of the appeal brief, appellants argue the rejection is incorrectly based on the grounds that the use of an invention as a tool for research is not a substantial use. Appellants state that only a limited subset of research uses are not substantial: those in which the only known use for the claimed invention is to be an object of further study, thus merely inviting further research. Appellants argue that nowhere in their cited case law is it stated or implied that a material cannot be patentable if it has some other, additional beneficial use in research. Appellants' arguments are not found persuasive.

As discussed above, whereas a scale or gas chromatograph has patentable utility as a research tool as providing a result that can be readily used and provides a specific benefit in currently available form, in this case, the claimed polynucleotide does NOT provide a specific benefit in currently available form and the use of the polynucleotide would require further experimentation as described above. The claimed polynucleotide is not disclosed as having a property that can be identifiably and specifically useful without further, additional experimentation. The claimed invention is, in fact, the object of further study, merely inviting further research. None of the asserted utilities for the claimed polynucleotide meets the three-pronged test of being specific, substantial and credible.

At the top of page 24 of the appeal brief, appellants argue the claimed invention has a beneficial use in toxicology testing, drug discovery, and disease diagnosis. Appellants argue the claimed polynucleotide is a tool not an object of research. Appellants argue the data generated as a result of gene expression monitoring using the claimed invention is not merely to study the polynucleotide itself, but to study properties of tissues, cells, and potential drug candidates and toxins. Appellants argue that without the claimed invention, information regarding properties of tissues, cells, and potential drug candidates and toxins is less complete. Appellants argue the use of the invention in toxicology testing is substantial and specific. Appellants argue that although all polynucleotides expressed in humans have utility for toxicology testing, this does not preclude the utility from being specific and substantial. Appellants argue a toxicology test using a particular polynucleotide is dependent on the identity of that polynucleotide. Appellants argue the result obtained from toxicology testing is specific to both the compound and polynucleotide being tested. Appellants argue no two human-expressed polynucleotides are interchangeable for toxicology testing due to the identity of the polynucleotide and it is not necessary to know the biological function and disease association of the polynucleotide in order to perform such toxicology tests. Appellants argue at the very least the polynucleotides are useful as controls for toxicology testing. Appellants' arguments are not found persuasive.

It is evident from the example of Shattuck-Eidens et al. that utility for a polynucleotide does not require knowledge of biological function. However, If any polynucleotide expressed in a human has utility in toxicology testing, then that polynucleotide has no *specific* utility as all polynucleotides would have

such use, regardless of the dependence on the identity of a given polynucleotide and therefore, does not satisfy the utility requirement of 35 USC § 101. In a related example, all polynucleotides have use as templates for protein expression. The encoded amino acid sequence for any given nucleic acid is specific and dependent upon the identity, i.e., nucleotide sequence, of the encoding nucleic acid. However, as *all* nucleic acids have utility for protein expression, this utility is not specific and therefore does not satisfy the utility requirement of 35 USC § 101. Furthermore, it is noted that the specification provides no guidance to allow a skilled artisan to use data relating to the claimed polynucleotides derived from the results of toxicology testing and what the results would mean. For example, if the claimed polynucleotides were attached to a microarray and used in toxicology testing or gene expression analysis and a result showed that expression was increased when a cell was treated with a particular agent, the specification provides no basis on which a skilled worker would be able to determine whether that result is meaningful. As such, further experimentation would be required to interpret the results of such gene expression analysis. Also, based on the specification and the Bedilion Declaration, one of ordinary skill in the art would recognize that knowledge of the function of the protein encoded by the claimed polynucleotide is necessary to be useful for therapeutic and diagnostic uses and gene expression monitoring in toxicology - even though such use is non-specific. The specification states, "[t]he discovery of proteins related to human renal sodium phosphate transport protein, and the polynucleotides encoding them, satisfies a need in the art by providing new compositions useful in diagnosis and treatment of diseases associated with increased or decreased phosphate levels" (page 2, bottom). The Bedilion Declaration states, "a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain any of these polynucleotides, in connection with conducting gene expression monitoring studies on... ...drugs for disorders associated with increased or decreased phosphate levels for such purposes as evaluating their efficacy and toxicity" (emphasis added; Bedilion Declaration, paragraph 15). Thus, as evidenced by the specification Bedilion Declaration, the biological function of the polypeptide encoded by SEQ ID NO:2 is indeed required for these utilities.

Beginning at the bottom of page 24 of the appeal brief, appellants present the example of a histone gene expressed in humans as having a specific and substantial use in toxicology testing.

Appellants argue a histone gene may not be a suitable therapeutic target, but the gene is allegedly an excellent subject for toxicology testing of drugs targeted to other genes. Appellants argue a drug that alters expression of a histone gene is toxic because disruption of said histone gene would have undesirable side effects. Appellants argue that a histone gene is a good measure of toxicity when analyzing compounds targeted to another gene because that histone gene cannot be replaced with a different gene and this measure of toxicity is independent of knowledge of the biological function or disease association of the histone gene. Appellants' arguments are not found persuasive.

Appellants erroneously attempt to compare a histone gene with the claimed polynucleotide. As one of ordinary skill in the art would recognize, histone is ubiquitously expressed, its function has been fully characterized, it is necessary for cell survival and function, and data from gene expression analysis demonstrating disruption in the expression of histone due to administration of a drug would clearly suggest undesirable side effects. This example is in no way related to the instant case. In contrast to the histone example, the function of the polypeptide encoded by SEQ ID NO:2 is wholly uncharacterized, the physiological implications of altered expression of SEQ ID NO:1-encoding polynucleotides is completely unknown, and the specification provides zero guidance for interpreting a result obtained from gene expression analysis with respect to toxicology testing. As previously stated, there is no indication of the effects of altered expression of the claimed nucleic acid in the specification and there is no indication as to how altered expression of the claimed polynucleotide would be useful, e.g., as a marker of toxicity of a compound. Thus, further experimentation is required for a real world use of the claimed invention and thus, the claimed invention has no substantial utility.

At the first full paragraph at page 25 of the appeal brief, appellants argue the expression of SEQ ID NO:1-encoding polynucleotides in human tissues would lead a skilled artisan to believe that these polynucleotides have some physiological implications, even if these implications have not been precisely defined. Appellants argue that during toxicology testing a change in expression of a polynucleotide indicates potential toxicity of a drug candidate, even if the polynucleotide is not absolutely necessary for cell survival and function and even if the physiological implications of that polynucleotide are unknown. Appellants argue the benefit of such a toxicology test is an increased chance of finding a safe and

effective drug and a corresponding reduction in time and expense of bringing a drug to market. Appellants' arguments are not found persuasive.

It is noted that the specification provides no guidance regarding the meaning of any observed results of altered expression of the claimed polynucleotides. It is noted that appellants state, "a change in expression of a human-expressed polynucleotide indicates potential toxicity of a drug candidate". In this case, the specification provides NO indication as to whether a change in the expression of the claimed polynucleotides indicates toxicity or not and what level of altered expression would result in toxicity – therefore, further experimentation would be required to interpret any result obtained from toxicology testing using the claimed polynucleotides. Thus, this utility is not substantial as it does not provide a specific benefit in currently available form. As stated above, this is in stark contrast to appellants' histone gene example, wherein the function of a histone protein is known, it is necessary for cell survival and function, and data from gene expression analysis demonstrating disruption in the expression of histone due to administration of a drug would clearly suggest undesirable side effects.

At the bottom of page 25 of the appeal brief, appellants argue if all of the class of expressed human polynucleotides can be used in toxicology testing, then they all have patentable utility. Appellant's argue the issue is whether the invention has any utility not whether other compounds have a similar utility. Appellants argue that nothing in the law says that an invention must have a "unique" utility and that the whole notion of "well-established" utility presupposes that many different inventions can have the exact same utility. Appellant argues that if the examiner's argument were correct, there could never be a "well-established" utility.

It is noted that appellants have never been asked to identify a utility that is unique, i.e., not shared by any other compounds or compositions. Rather, appellants have been required to identify a utility that is specific to the invention claimed, as opposed to one that would apply regardless of the specific properties of the claimed invention. An invention certainly can have a utility that is shared by other compounds or compositions. On the other hand, not every utility will satisfy 35 USC § 101, even if the utility is shared by a class of inventions. So while a utility need not be unique to a claimed invention, it must nonetheless be specific, and in currently available form, in order to satisfy § 101. Here, appellants assert that any

expressed human polynucleotide can be used in toxicology testing. However, as stated above, any observed results of altered expression of the claimed polynucleotide would have no meaning without additional knowledge of what this change in expression means. The specification in effect discloses that the claimed products can be put on microarrays, and appellants assert those of skill in the art can figure out how to use them for toxicology testing. This utility is not substantial; it does not provide a specific benefit in currently available form. Assuming *arguendo* that a generic microarray—one comprising thousands of uncharacterized or semi-characterized gene fragments—would provide a useful tool for, e.g., toxicology testing, it does not follow that each one of the human expressed polynucleotides represented in the microarray individually has patentable utility. Although each polynucleotide in the microarray contributes to the data generated by the microarray overall, the contribution of a single gene—its data point—is only a tiny contribution to the overall picture. The patentable utility of a microarray, for example, does not necessarily mean that each tiny component of the microarray also has patentable utility. A patentable utility divided by a thousand does not necessarily equal a thousand patentable utilities. Each claimed invention must be shown to meet the utility requirement of 35 USC § 101 in order to be patentable; it must provide a specific benefit in currently available form. Providing a single data point among thousands or millions, even if the thousands or millions of data points collectively are useful, does not meet this standard.

At the first full paragraph at page 26, appellants argue the claimed invention has numerous additional uses as a research tool, each of which is a substantial utility such as diagnostic assays and chromosomal mapping.

In regards to appellants' asserted use of the claimed polynucleotide for chromosomal mapping, it is noted that any human polynucleotide can be used for chromosomal mapping – this utility is not specific. Regarding appellants' asserted use of the claimed polynucleotide for diagnostic assays, in order for a polynucleotide to be useful, as asserted, for diagnostic assay, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in tissue that is derived from brain tumor cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or

causal relationship between the expression of the claimed polynucleotide and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many polynucleotides are expressed at equal levels and in identical forms in both normal *and* diseased tissues. Therefore, one necessarily needs to know, e.g., that the claimed polynucleotide is either present only in brain tumor tissue to the exclusion of normal tissue or is expressed in higher levels in brain tumor tissue compared to normal tissue. Evidence of a differential expression *might* serve as a basis for use of the claimed polynucleotides as a diagnostic for disease(s). However, in the absence of any disclosed relationship between the claimed polynucleotides or encoded proteins and any disease or disorder and the lack of any correlation between the claimed polynucleotides or the encoded proteins with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. Also, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form and would thus require further research for its implementation. Thus, the disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. § 101.

D. The Patent Examiner allegedly failed to demonstrate that a person skilled in the art would reasonably doubt the utility of the claimed invention.

At page 26 of the appeal brief, appellants argue the claims have been rejected based principally on citations to scientific literature identifying some of the difficulties in predicting protein function. Appellants state that it is incorrect to question whether utility can be imputed to the claimed invention based on its homology to another polypeptide. Appellants characterize the cited literature as not being inconsistent with appellants' alleged "proof" of homology by a reasonable probability. Appellants argue that the examiner has not made a showing that the assertion of utility cannot be accepted as true based

on evidence that a person of ordinary skill would doubt the asserted utility by a reasonable probability. Appellants' arguments are not found persuasive.

It is noted that, while appellants have demonstrated "proof of homology" at the amino acid level (of only 48% identity), there is in fact no compelling evidence to demonstrate that the polypeptide encoded by SEQ ID NO:2 functions as a phosphate transporter. Neither the specification nor any evidence of record provides a functional characterization of the polypeptide encoded by SEQ ID NO:2 and appellants would rely only on an alleged "rule" proposed by Brenner et al. (1999) – which, as discussed above, does not apply in the instant case – to provide the basis of determining the function of NAPTR. The references of Brenner (1999) and Scott et al. have been cited as references that provide the state of the art regarding functional assignment based solely on structural features. Brenner (1999) states, "[w]ithout laboratory experiments... ...it is impossible to know for certain [whether the function assigned to a protein by annotation is correct]" (page 132, left column, second paragraph). Scott et al. (*Nat Genet* 21:440-443) teach "the importance of confirming the function of newly identified gene products even when database searches reveal significant homology to proteins of known function" (page 441, left column, third full paragraph). The cited references demonstrate that empirical evidence is *required* to demonstrate and confirm biological function – particularly in the instant case where there is *only* 48% amino acid sequence identity between NAPTR and NPT1. In this case, there is no evidence of record to suggest that NAPTR has *any* biological activity and the protein may just as well be non-functional.

Beginning at the bottom of page 26 of the appeal brief, appellants argue the references cited by the examiner fail to support the outstanding rejection. Appellants cite Brenner et al. (1998) as evidence that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Appellants argue the Office must accept appellants' demonstration that the homology between NAPTR and NPT1 demonstrates utility by the "reasonable correlation" standard as set by case law. Appellants' arguments are not found persuasive.

As stated above, appellants improperly attempt to extrapolate the results of Brenner et al. (1998) to the asserted 48% amino acid sequence identity between NAPTR and NPT1. The study of Brenner et

al. (1998) has been conducted to identify distant evolutionary homology using sequence comparison algorithms. Nowhere does Brenner et al. state their results can be extrapolated for use in predicting functional homology. Brenner et al. (1998) clearly state that these comparisons "have been assessed using proteins whose relationships are known reliably from their structures and functions, as described in the SCOP database" (page 6073, abstract). The art recognizes the proteins within the SCOP database have been *fully characterized* – functionally by empirical laboratory experiments and structurally by generating at least one three-dimensional structure of the proteins (see for example Murzin et al. In this case, appellants quote a portion of Brenner et al. (1998) out of context and attempt to use these teachings to inappropriately support their argument. Brenner et al. (1998) are silent as to the use of their results to the functional assignment of a functionally uncharacterized protein. Thus, the results of Brenner et al. (1998) are not relevant to a functional assignment of NAPTR. Contrary to appellants' assertion, there is no "reasonable correlation" between the results of Brenner et al. (1998) and the functional assignment of NAPTR based solely on 48% sequence homology to NPT1. Instead, regarding functional assignment based on sequence homology, Brenner (1999) teaches that laboratory experiments are required to verify a protein's function (page 132, left column, second paragraph), which clearly is not the case here. The reference of Brenner et al. (1998) fails to demonstrate the claimed invention has *any* patentable utility.

Beginning at the bottom of page 27 of the appeal brief, appellants argue that, contrary to the examiner's assertions, the use of sequence comparison to predict protein function is supported by Bork (Genome Research 10:398-400) who allegedly discloses a 70% accuracy rate in bioinformatics-based predictions and a 90% accuracy rate when predicting functional "features". Appellants argue that based on this teaching, a skilled artisan would more likely than not believe the asserted utility. Appellants argue even if the numbers of Bork are "crude estimates" and "overestimates", they are nonetheless Bork's best estimates for predicting accuracy. Appellants argue Bork's numbers were still the best test sets available in the literature, and are indicative of the state of the art at that time. Appellants argue that the reference of Bork supports the notion that a skilled artisan would consider functional annotation by sequence homology to more likely than not be accurate. Appellants' arguments are not found persuasive.

Bork clearly states that gene annotation has a "considerable" error rate and further states that the evidence provided is a crude estimate and that "numbers in Table 1 are often overestimates because the test sets used are usually not representative of all sequences". Furthermore, Bork fails to demonstrate the claimed invention has *any* patentable utility. Based on the teachings of Brenner and Scott et al., one of ordinary skill in the art would recognize that the function of the polypeptide encoded by SEQ ID NO:2 cannot be assigned based on structure alone and further experimentation is required to assign the function of the encoded polypeptide. One of skill in the art would recognize that functional assignment based on sequence alone is highly dependent upon the proteins being compared and appellants have taken the position that any general reference is proof of their assertions, even when these references do not address the encoded proteins at issue. However, the examiner has cited a closely related reference – that of Scott et al. This reference is highly related to the instant case in terms of both the degree of homology (45% in the case of Scott et al. and 48% in the instant application) and the function of the proteins (homology suggested the protein of Scott et al. would be a sulfate transporter). Instead, appellants apply generalized references that are not relevant to the instant case and provide no additional information as to whether NAPTR is indeed a phosphpate transporter – we know nothing more about the encoded polypeptide or its utility after reading Brenner et al. (1999) and Bork as we did before.

Beginning at the middle of page 28 of the appeal brief, appellants criticize the references of van de Loo et al., Broun et al., and Seffernick et al. Appellants argue these references, while demonstrating the difficulty in obtaining a precise functional assignment, do not contradict the findings of Bork that, in the majority of cases, protein function is accurately predicted by sequence homology. Appellants argue the cited references do not provide any evidence that a skilled artisan would more likely than not doubt that NAPTR possesses the utility of NPT1 phosphate transporter. Appellants' arguments are not found persuasive.

It is noted that the instant claims are drawn to nucleic acids encoding NAPTR, not NPT1, therefore, the utility of NPT1 has not been questioned as nucleic acids encoding NPT1 are not the subject of the instant application – particularly in view of appellants' failure to provide *any* functional characterization of the polypeptide encoded by SEQ ID NO:2 as a phosphate transporter. It is further

noted that the utility of NPT1 is not at issue, and even assuming *arguendo* that the utility of NPT1 were at issue, there is no evidence of record of an asserted specific and substantial or well-established utility for NPT1. If an NAPTR-encoding nucleic acid had been claimed and elected for examination in the instant application, the examiner would fully analyze claims drawn to an NPT1-encoding nucleic acid under 35 U.S.C. § 101. As such claims drawn to nucleic acids encoding NPT1 are not present, the utility of NPT1 has not been questioned as it is not at issue. Instead, it is the utility of the claimed polynucleotides that is at issue. Also, as previously stated, appellants have mischaracterized the teachings of Bork as relative to *all* functional assignments, which they clearly are not. Bork teaches that gene annotation has a "considerable" error rate and further teaches their evidence is a crude estimate and that "numbers in Table 1 are often overestimates because the test sets used are usually not representative of all sequences". Furthermore, the reference of Bork fails to demonstrate the claimed invention has *any* patentable utility.

Appellants argue Seffernick et al. recognize that functional assignment based on >50% are considered to be reasonably sound and proteins with >98% sequence identity catalyzing different reactions is highly exceptional. Appellants argue this supports the argument that while a number of examples of incorrect assignment of function, this does not contradict the findings of Bork et al. who, appellants allege, teach that in general, sequence homology is an accurate method for assigning biological function. Appellants argue the teachings of Bork do not show that errors cannot occur, but that there may be difficulties in predicting function based on sequence.

Appellants' arguments are not found persuasive. It is noted that appellants' statement by Seffernick et al. regarding >50% sequence identity has been mischaracterized. In fact, Seffernick et al. teach their result of identifying two proteins with >98% identity and having distinct functions "underlies current genome annotation efforts where functional assignments based on >50 % sequence identity are considered to reasonably sound" (page 2409, left column, middle) – thus, supporting the examiner's argument that sequence identity is not predictive of function. While it is acknowledged that Seffernick describe their findings as "highly exceptional", this reference nonetheless provides evidence that functional assignment cannot be based on sequence identity alone and should be substantiated by

empirical evidence. This is further evidenced by Scott et al. who teach a polypeptide that has 45 % sequence identity (it is noted that SEQ ID NO:1 similarly shares 48 % identity with NPT1) with a human sulfate transporter and that, based on structural homology has been proposed to function as a sulfate transporter (page 440, left column, abstract). However, an empirical analysis of the protein measuring its ability to transport various ions revealed the protein is actually a chloride-iodide transport protein (page 441, left column, third full paragraph). Scott et al. "conclude that pendrin does not function as a sulfate transporter, as suggested by its close homology to other sulfate transporters, but instead functions as a sodium-independent transporter of chloride and iodide. These results underscore the importance of confirming the function of newly identified gene products even when database searches reveal significant homology to proteins of known function" (emphasis added; page 441, left column, third full paragraph). Thus, based on this evidence, the person of ordinary skill in the art would *reasonably* doubt whether the polypeptides encoded by the claimed polynucleotides have a functions similar to NPT1, a phosphate transport protein. Regarding the reference of Bork, it is noted that Bork recognizes that gene annotation has a "considerable" error rate and states their evidence provided is a crude estimate and that "numbers in Table 1 are often overestimates because the test sets used are usually not representative of all sequences". Furthermore, the reference of Bork fails to demonstrate the claimed invention has *any* patentable utility. Provided the supporting evidence, it is submitted that one skilled in the art would have had substantial reason to doubt the assertion that the claimed polynucleotides encode a polypeptide having function similar to NPT1 or the family of phosphate transport proteins. As previously stated, one of skill in the art would recognize that functional assignment based on sequence homology is highly dependent upon the proteins being characterized and appellants have taken the position that any general reference is proof of their assertions, even when these references do not address the encoded proteins at issue. However, the examiner has cited a closely related reference – that of Scott et al. This reference is highly related to the instant case in terms of both the degree of homology (45% in the case of Scott et al. and 48% in the instant application) and the function of the proteins (homology suggested the protein of Scott et al. would be a sulfate transporter). Instead, appellants apply generalized references that provide no additional information as to whether the polypeptide encoded by SEQ ID NO:2 is indeed a phosphpate

transporter. Nothing more is known about NAPTR in view of the teachings of Brenner et al. (1998) and Bork or any other cited reference. Appellants have, in fact, failed to demonstrate that NAPTR is a phosphate transport protein and has patentable utility and would instead attempt to "prove" function by way of generalized references that provide no further information of the function of NAPTR.

At the bottom of page 30 of the appeal brief, appellant argues the examiner misunderstands the significance of the shared N-glycosylation site in characterizing the SEQ ID NO:1 polypeptide as it is both the presence and location of the N-glycosylation site makes it significant. Appellant argues the conservation of the location of the single N-glycosylation site among the three proteins confirms the finding that NAPTR possesses the utilities of the phosphate transporters. Appellants' arguments are not found persuasive.

Again, appellants rely solely on structural features to confirm a finding and attempt to rely on these solely structural features to relate the utility of NAPTR to NPT1 or rat brain-specific sodium dependent phosphate cotransporter (whatever these utilities may be as there are no well-established utilities for either of the proteins). As stated above and disclosed in the specification, this is a *predicted* N-glycosylation site. Appellants have provided no evidence to suggest that it is indeed an N-glycosylation site and without such confirmation, there is no way of knowing whether this is an actual N-glycosylation site. Even assuming *arguendo* this was an actual N-glycosylation site, the fact remains that the specification fails to provide *any* functional characterization of the polypeptide encoded by SEQ ID NO:2 that would indicate that it is a phosphate transporter.

Beginning at the top of page 31 of the appeal brief, appellants argue because the proteins of Vrlijic et al. are all transporter proteins which function in solute export is evidence that similar hydrophobicity plots can be a useful indicator of similar biological function and would support their argument that based on similar hydrophobicity plots between NAPTR and NPT1, the proteins would share phosphate transporter function. Appellants' argument is not found persuasive.

The proteins of Vrlijic et al. transport *different* solutes, i.e., the proteins have different biological functions. Appellants mistakenly attempt to generalize the biological functions ("solute export") of the proteins compared by Vrlijic et al. to support their argument. One could just as easily generalize the

findings of Scott et al. – a sulfate transporter and a sodium-iodide transporter are both "solute export" proteins – however, each the proteins has a distinct biological function as acknowledged by Scott et al.

At the middle of page 31 of the appeal brief, appellants address the reference of Tenenhouse et al. arguing the examiner ignores the fact that both of these proteins have utility in transporting phosphate based on the function of the proteins, not their differential expression. Appellants' argument is not found persuasive.

It is noted that appellant states, "[NPT1 and NPT2] have utility in transporting phosphate" and "[t]his utility is based on the phosphate transport function of these proteins" – however, it is unclear as to what utility these proteins have. While the utility of the claimed polynucleotides and not the utility of NPT1 and NPT2 is at issue, it is noted that there is no well-established utility for either of NPT1 and NPT2 and appellants have yet to provide evidence to demonstrate that such exists. Instead, the examiner cited Tenenhouse et al. as an example to demonstrate a point – that even *polynucleotides* encoding polypeptides with similar functions do not necessarily have similar utilities. For example, if the polynucleotide encoding NPT1 was shown to be a disease marker, this in itself would provide no evidence that the polynucleotide encoding NPT2 would also be a disease marker. Thus, polynucleotides encoding polypeptides having similar function do not necessarily have similar utility.

At the bottom of page 31 of the appeal brief, appellants argue the examiner's criticisms of Brenner et al. (1998) are inapt. Appellants argue the use of the SCOP database by Brenner et al. (1998) makes their findings more reliable and that any general findings are robust and reliable. Appellants argue the "rules" derived by Brenner et al. (1998) are ideal for addressing a situation such as this. Appellants argue the teachings of Brenner et al. (1998) can be applied to any other uncharacterized proteins. Appellants argue if it were necessary to compare fully characterized proteins before analysis, there would be no need for such analysis. Appellants argue there is no need for empirical characterization or three-dimensional structural analysis to apply the "rules" of Brenner et al. (1998).

As stated above, appellants improperly attempt to extrapolate the results of Brenner et al. (1998) to the asserted 48% amino acid sequence identity between NAPTR and NPT1. The study of Brenner et al. (1998) has been conducted to identify distant evolutionary homology using sequence comparison

algorithms. Nowhere does Brenner et al. state their results can be extrapolated for use in predicting functional homology. Furthermore, Brenner et al. (1998) clearly state that their comparisons "have been assessed using proteins whose relationships are known reliably from their structures and functions, as described in the SCOP database" (page 6073, abstract). The art recognizes the proteins within the SCOP database have been *fully characterized*, meaning their functions have been characterized by empirical laboratory experiments and their three dimensional structures have been generated (see for example Murzin et al. Brenner et al. (1998) are silent as to the use of their results to the functional assignment of an uncharacterized protein. In this case, appellants quote a portion of Brenner et al. (1998) out of context and attempt to use these teachings to inappropriately support their argument. In fact, the results of Brenner et al. (1998) are applicable ONLY for identifying evolutionary homology – not functional homology. Even assuming *arguendo* that the results of Brenner et al. (1998) could be applied to functional annotation – which they cannot – it is unclear as to whether these results would be applicable to an uncharacterized protein as Brenner et al. (1998) teach their results are specific for the database used in the study by stating, "30% identity is a reliable threshold for [the PDB90D-B database]" and that, "40% is a reasonable threshold, for a database of this particular size and composition". In the instant case, neither the specification nor the prior art provides a functional characterization of NAPTR and there is no evidence of record that NAPTR has phosphate transporter function and *it is just as likely that NAPTR has no function at all.* Thus, there is no "reasonable correlation" between the results of Brenner et al. and the functional assignment of NAPTR based solely on 48% sequence homology to NPT1. Instead, Brenner (1999) teaches that laboratory experiments are required to verify a protein's function (page 132, left column, second paragraph), which clearly is not the case here. It is further noted that the reference of Brenner et al. (1998) fails to demonstrate the claimed invention has *any* patentable utility.

At the middle of page 32 of the appeal brief, appellants argue the examiner ignores the findings of Brenner et al. (1998) that 30% identity over 150 amino acids or 40% identity over 70 amino acids is an indicator of homology. Appellants argue that no support has been given to support the examiner's assertion that 48% identity over 401 amino acids is low sequence identity. Appellants argue the examiner is incorrect in asserting the function of NAPTR has been assigned based solely on sequence identity as

the proteins share a potential N-glycosylation site at the same location and have similar hydrophobicity plots. Appellants' arguments are not found persuasive.

As previously stated, appellants quote a portion of Brenner et al. (1998) out of context and attempt to use these teachings to inappropriately support their argument. In fact, the results of Brenner et al. (1998) are applicable ONLY to the PDB90D-B database used by Brenner et al. (1998). Brenner et al. (1998) clearly state, "30% identity is a reliable threshold for this database" and that, "40% is a reasonable threshold, for a database of this particular size and composition". The results of Brenner et al. (1998) support a finding that 30% identity over 150 amino acids or 40% identity over 70 amino acids is an indicator of evolutionary homology – not functional homology. Brenner et al. (1998) are silent as to the use of their results to the functional assignment of a functionally uncharacterized protein. Again, appellants rely solely on structural features to confirm function and attempt to rely on these solely structural features to relate the utility of NPT1 to NAPTR or rat brain-specific sodium dependent phosphate cotransporter (whatever these utilities may be as there are no well-established utility for NPT1). As stated above and disclosed in the specification, this is a *predicted* N-glycosylation site. Appellants have provided no evidence to suggest that it is indeed an N-glycosylation site and without such confirmation, there is no way of knowing whether this is an actual N-glycosylation site. Even assuming *arguendo* this was an actual N-glycosylation site, the fact remains that the specification fails to provide *any* functional characterization or patentable utility of the polypeptide encoded by SEQ ID NO:2. The proteins of Vrlijic et al. transport *different* solutes, i.e., the proteins have different biological functions. Appellants attempt to generalize the biological functions ("solute export") of the proteins compared by Vrlijic et al. to support their argument. One could just as easily generalize the findings of Scott et al. – a sulfate transporter and a sodium-iodide transporter are both "solute export" proteins – however, each the proteins has a distinct biological function as acknowledged by Scott et al.

At the bottom of page 32 of the appeal brief, appellants argue the question is not whether biological function can be predicted with certainty based on sequence, but rather the question is whether the claimed invention meets the utility requirements under 35 U.S.C. § 101. Appellants argue the examiner would seem to apply a standard that calls for a skilled artisan to be certain of the asserted

utility, with no margin for error. Appellant argues the standard is whether an ordinarily skilled artisan would more likely than not believe the asserted utility and appellants assert this standard has been met. Appellants argue the examiner's references are isolated examples and that, in contrast to the references of Brenner et al. (1998) and Bork, are generally applicable to functional assignment based on amino acid sequence. Appellant argues that as the cited references are insufficient to support the rejection, the rejections must be reversed. Appellant argues the only evidence of record shows that one would not doubt the encoded polypeptide is in fact a member of family of phosphate transporters, which are known to have specific utility. Appellants' arguments are not found persuasive.

The examiner agrees that the issue at hand is whether the claimed polynucleotide has patentable utility. However, the issue of the function of NAPTR is relevant to the instant rejection as appellants attempt to relate the function of NPT1, a known phosphate transporter, to NAPTR, a functionally uncharacterized protein, and further attempt to relate the utility of NPT1 to NAPTR (see for example, page 22, last paragraph). Appellants have failed to functionally demonstrate NAPTR is a phosphate transporter, and have similarly failed to demonstrate NAPTR has the same utility as NPT1 (whatever that utility may be as there is no well-established utility for NPT1). Furthermore, as previously stated, a skilled artisan recognizes the fallacy in applying the general teachings of Brenner et al. (1998) and Bork to functionally demonstrating biological activity. These references are silent in regards to determining whether a protein actually has biological activity and it is just as likely that NAPTR has no biological activity as there is no evidence of empirical demonstration of *any* biological activity of NAPTR. The references cited by the examiner show that functional assignment based on homology, while useful for suggesting an encoded protein's function, must be verified by empirical analysis and in the instant case appellant has failed to provide such empirical evidence. Furthermore, neither Brenner et al. (1998) nor Bork demonstrate the claimed invention has *any* patentable utility.

IV. By requiring the patent appellant to assert a particular or unique utility, the patent examination utility guidelines and training materials applied by the patent examiner allegedly misstate the law.

Beginning at the bottom of page 33 of the appeal brief, appellants challenge the legality of the Patent Examination Utility Guidelines. Appellants argue that "unique" or "particular" utilities have never been required by the law and appellants are unaware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Appellants argue that to meet the utility requirement, the invention need only by "practically useful" and confer a "specific benefit" on the public. Appellants' arguments are not found persuasive.

Regarding the Training Materials, appellants are reminded that the examiner must examine a patent application according to the guidelines set forth by the USPTO as well as the MPEP, since the examiner has no authority to disregard such guidelines or to apply his own interpretation of patent law in the examination of the application. Furthermore, as set forth in the guidelines and the MPEP, the guidelines were promulgated by the Patent Office in accordance with all applicable case law and thus are believed to be consistent therewith. Appellants are further reminded that the examiner has no authority to comment in regard to the legality of the new utility guidelines or the MPEP as set forth by the USPTO. Accordingly, it is the examiner's position that the instant claims, based on an analysis of the utility requirement of 35 USC § 101 and following the current Utility Guidelines, have no specific, substantial, or credible utility.

Regarding appellants' comments regarding a "unique" utility, it is noted that appellants' characterization of the examiner's position is somewhat misleading. Appellants have never been asked to identify a utility that is unique, i.e., not shared by any other compounds or compositions. Rather, appellants have been required to identify a utility that is specific to the invention claimed, as opposed to one that would apply regardless of the specific properties of the claimed invention. An invention certainly can have a utility that is shared by other compounds or compositions. While a utility need not be unique to a claimed invention, it must nonetheless be specific, and in currently available form, in order to satisfy 35 USC § 101.

Written Descripti n Rejection Under 35 USC § 112, First Paragraph

Beginning at the bottom of page 35 of the appeal brief, appellants traverse the examiner's assertion that the single disclosed species of the genus of claimed polynucleotides, i.e., SEQ ID NO:2, fails to represent the entire genus of claimed polynucleotides. Appellants cite case *Vas-Cath, Inc. v. Mahurkar,* 19 USPQ2d 1111, 1117 (Fed Cir 1991) and the "Guidelines for Examination of Patent Applications" for written description and assert that the written description standard is fulfilled by what is specifically disclosed and what is well-known in the art.

A. The specification does not provide an adequate written description of the claimed "variants" and "fragments" of SEQ ID NO:1 and SEQ ID NO:2.

Beginning at the bottom of page 36 of the appeal brief, appellants argue the claimed subject matter is either disclosed or is conventional or well known to a skilled artisan and provide alleged support for the "variants" and "fragments" as encompassed by the claims. Appellants argue that a skilled artisan would recognize polynucleotide sequences that are variants having a sequence at least 90% or 95% identical to SEQ ID NO:2, or which encode polypeptide variants having an amino acid sequence at least 90% identical to SEQ ID NO:1. Appellants argue that given a naturally-occurring polynucleotide sequence, it would be routine for a skilled artisan to recognize whether it is a variant of SEQ ID NO:2 or encoded a variant of SEQ ID NO:1. Based on this alleged "routine recognition", appellants conclude that the specification provides an adequate description of the claimed variants of SEQ ID NO:2 or polynucleotides encoding variants of SEQ ID NO:1. Similarly, appellants argue that a skilled artisan would recognize polynucleotides that are fragments of SEQ ID NO:2 or encode polypeptides that are fragments of SEQ ID NO:1. Appellants argue the sequences of SEQ ID NO:1, 2, and 5 provides the necessary framework for the recited fragments and that to recite all possible fragments would needlessly clutter the application. Appellants argue it would be routine for a skilled artisan to determine those fragments of SEQ ID NO:1 having phosphate transport activity using the disclosed assay. Based on this disclosure, appellants conclude that the specification provides an adequate description of the claimed fragments of

SEQ ID NO:2 or polynucleotides encoding fragments of SEQ ID NO:1. Appellants' arguments are not found persuasive.

The specification provides *only a single representative species* of the claimed genus of nucleic acids, i.e., the nucleic acid of SEQ ID NO:2 encoding a polypeptide asserted as having phosphate transport activity. The single disclosed representative species of SEQ ID NO:2 fails to provide an adequate description of the entire genus of claimed variants of SEQ ID NO:2, nucleic acids encoding variants of SEQ ID NO:1, or nucleic acids comprising fragments of SEQ ID NO:2. Appellants' alleged description of variants of SEQ ID NO:2 and nucleic acids encoding variants of SEQ ID NO:1 and nucleic acids comprising fragments of SEQ ID NO:1 (see page 36, lines 8-18) merely provides a textual description of said variants and nucleic acids comprising fragments and provides no additional structures of representative species. As such, a skilled artisan would *not* be able to visualize the structures of each member of the claimed genus. Because there is no functional limitation provided for the variants of SEQ ID NO:2 and nucleic acids encoding variants of SEQ ID NO:1, one of skill in the art would recognize that the claimed genus of variants encompass species having substantial functional variation within the genus. Similarly, one of skill in the art would recognize that the claimed genus of nucleic acids *comprising* only 20 or 60 nucleotides of SEQ ID NO:2 encompass species having substantial structural and functional variation within the genus. One of skill in the art would recognize that such variants encompass nucleotide sequences encoding polypeptides having the asserted phosphate transport activity in addition to non-functional polypeptides and polypeptides having function other than the asserted phosphate transport activity. When there is substantial variation within a genus, one must describe a sufficient variety of species to reflect the variation within the genus. One of skill in the art would recognize that – due to the substantial variation of species within the genus - it is highly unpredictable as to whether all species within the genus will encode polypeptides having the asserted phosphate transport activity. For inventions in an unpredictable art, adequate description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus. Therefore, the single representative species of SEQ ID NO:2 fails to describe the entire genus of claimed nucleic acid variants and nucleic acids *comprising* fragments of SEQ ID NO:2.

1. The recitati n of chemical structure fails t specifically define th speci s within the claimed genus.

Beginning at the middle of page 38 of the appeal brief, appellants summarize case law citing *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed Cir 1993) and *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed Cir 1997) as court cases in which the recitation of functional characteristics of a DNA, without description of structural features has been a basis by which the courts have found invalid claims to DNA. Appellants argue the claims at issue are in contrast to the claims of the *Lilly* and *Fiers* cases as appellants allege the claimed genus of nucleic acids is defined by structure rather than function. Appellants argue there is no reliance solely on functional characteristics of the claimed nucleic acids. Appellants argue the Office has failed to base the written description inquiry "on whatever is now claimed" and fails to provide an appropriate analysis of the instant claims and how they differ from those of the *Lilly* and *Fiers* cases. Appellants argue the Guidelines indicate that evidence of possession includes structure, physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of such characteristics. Appellants assert the claimed polynucleotides have been described by chemical structure, physical properties, and chemical properties and conclude that the written description requirement has been met. Appellants' arguments are not found persuasive.

While it is acknowledged that the current claims differ from the *Lilly* and *Fiers* cases, as discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show appellants were in possession of the claimed genus. A representative number of species means that the species that are adequately described are representative of the entire genus. The specification discloses only a single representative species of the claimed genus, i.e., SEQ ID NO:2. Further, as stated above, there is substantial variation within the structure and/or function of the genus of

claimed nucleic acids. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. At the time of the invention, one of skill in the art would recognize the absence of the ability to predict the function(s) of all species of claimed nucleic acids. For inventions in an unpredictable art, adequate written description of a genus that embraces widely variant species cannot be achieved by disclosing only one species within the genus. As described above, one of skill in the art would recognize that the claimed genus of variants encompass species having substantial variation of function within the genus and would recognize that the claimed genus of nucleic acids *comprising* only 20 or 60 nucleotides of SEQ ID NO:2 encompass species having substantial variation of structure and function within the genus. As such, neither the description of the structure and function of SEQ ID NO:2 nor the disclosure of solely structural features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus of claimed polypeptides.

The examiner disagrees with appellants' assertion that the claimed genus of polynucleotides of claim 3 part b); 12 parts b), d), and e); claim 13; claim 57 parts b), d), and e); and claim 58 have been sufficiently described by structure, physical properties, and chemical properties. The claimed genus has been described ONLY by a structural feature and the single disclosed species of SEQ ID NO:2 fails to represent all members of the claimed genus.

2. The present claims define a genus which is highly variant.

Beginning at the top of page 41 of the appeal brief, appellants argue the claims do not recite a genus that is highly variant. Appellants argue that available evidence indicates that the claimed genus is of narrow scope. In support of appellants' assertion, they rely on the teachings of Brenner et al. (1998). Appellants argue that, based on the teachings of Brenner et al., naturally-occurring molecules may exist that could be characterized as having phosphate transport activity with only 30% identity over 150 amino acid residues of SEQ ID NO:1. Appellants argue the claims recite a nucleic acid encoding a naturally-occurring amino acid sequence with at least 90% identity to SEQ ID NO:1, which has 401 amino acids. Appellants assert this variation is far less than those phosphate transporters having as little as 30% identity over at least 150 residues of SEQ ID NO:1. Appellants argue that all that is required to satisfy the

written description requirement is that one of skill in the art would reasonably conclude that appellants were in possession of the claimed genus at the time of the invention. Appellants argue that Brenner et al. (1998) provide reasonable guidelines for judging homology and that even if these guidelines are not 100% accurate, they nonetheless would lead a skilled artisan to understand that proteins meeting the criteria of Brenner et al. (1998) would likely share similar function. Appellants' argument is not found persuasive.

As stated above, appellants improperly attempt to apply the teachings of Brenner et al. (1998) to support their argument. The study of Brenner et al. (1998) has been conducted to identify distant evolutionary homology using sequence comparison algorithms. Nowhere does Brenner et al. state their results can be extrapolated for use in predicting functional homology. Even assuming *arguendo* that the results of Brenner et al. (1998) were applicable to the determination of the function of NAPTR – which they are not – one of skill in the art would recognize that the teachings of Brenner et al. (1998) cannot be used in a wholesale fashion to assign function to any and all proteins only because they meet the criteria as set forth by Brenner et al. (1998) as evidenced by van de Loo et al., Seffernick et al., Broun et al., and Scott et al., who teach homology between protein sequences – even at a particularly high level – is not indicative of identical function. Here, appellants have failed to provide convincing evidence that NAPTR itself is a phosphate transporter. Thus, it is unpredictable as to whether even those sequences encoding polypeptides sharing a relatively high degree of sequence homology with NAPTR with have phosphate transport activity. Thus, the teachings of Brenner et al. (1998) fail to support appellants' argument that the genus of claimed polynucleotides is not highly variant. Brenner (1999) teaches that it is impossible to know the accuracy of functional assignment without empirical laboratory evidence (page 132, left column, second paragraph). In this case, appellants have failed to provide such evidence and therefore, it is highly unpredictable as to whether *any* of the species of polynucleotides encompassed by the claimed genus will exhibit the asserted phosphate transport activity. However, even assuming *arguendo* that NAPTR has phosphate transport activity, as the genus encompasses widely variant species, the single disclosed species of SEQ ID NO:2 fails to describe all species encompassed by the claimed genus.

3. Advances in the state of the art fr m the time of *Lilly* and *Fiers* d n t obviate sufficient written descripti n of the claimed inventi n.

Appellants argue the state of the art at the time of the invention is further advanced than at the time of the *Lilly* and *Fiers* cases. Appellants argue the techniques and technological advances since the *Lilly* and *Fiers* up to the filing of the instant application in combination with the teachings provided in the instant specification are such that one of skill in the art would recognize that appellants were in possession of the claimed polynucleotide variants and fragments. Appellants' arguments are not found persuasive.

While advances in the art are undeniable and widely recognized, the point of the rejection is lack of written description and not lack of enabling disclosure. The state of the art still does not allow one of skill in the art to predict the structure and function of naturally-occurring variants or nucleic acids comprising fragments of SEQ ID NO:2 based solely on a single disclosed polynucleotide structure. Most importantly, one skilled in the art would not be able to divine the functions of other naturally-occurring sequences or nucleic acids comprising fragments of SEQ ID NO:2 based on the knowledge of the asserted function of only one disclosed species. For inventions in an unpredictable art, adequate written description of a genus that embraces widely variant species cannot be achieved by disclosing only one species within the genus.

Scope of Enablement Rejection Under 35 USC § 112, First Paragraph

Beginning at the top of page 44 of the appeal brief, appellants argue that the polypeptide variants encoded by the nucleic acid of claim 3 are "naturally-occurring" and that through the process of natural selection, nature will have determined the "appropriate" amino acid sequences. Appellants argue it is routine experimentation to obtain those nucleic acids encoding the recited variants. Appellants argue that using the common nucleic acid isolation techniques of hybridization or PCR, a skilled artisan need not make and test vast numbers of nucleic acids, and instead need only use said techniques to identify those relevant variant-encoding polynucleotides that exist in nature. Appellants argue that, by extension, one of skill in the art could use fragments of variants of SEQ ID NO:2 as hybridization probes and optionally as

arrays to detect full length polynucleotides. Appellants argue that it is not necessary for a polynucleotide to encode a functional polypeptide for one of skill in the art to be able to use that polynucleotide without undue experimentation. Appellants argue the claimed polynucleotides variants can be used in toxicology testing in drug discovery in order to detect toxic side effects. Appellants' arguments are not found persuasive.

The claims encompass nucleic acids encoding variants and nucleic acids comprising fragments that have the asserted phosphate transport activity in addition to variant polypeptides that are non-functional or exhibit a function other than the asserted phosphate transport activity. While techniques for isolation of nucleic acids encoding variants are known in the art, other than a method for screening those nucleic acids encoding polypeptides having the asserted phosphate transport activity, the specification provides no additional guidance in the form of assays for identifying those encoded proteins having activities other than the asserted phosphate transport. There are no working examples of variants of the SEQ ID NO:2 or nucleic acids encoding variants of SEQ ID NO:1. Furthermore, there is no guidance provided in the specification as to what *all* nucleic acids encoding variant polypeptides can be used for – particularly those variants encoding non-functional polypeptides. Appellants argue that polynucleotides encoding non-functional polypeptides can be used to detect polynucleotides encode NAPTR. However, the claims are not limited to those polynucleotides having substantially similar structures that would be so useful – see for example, the polynucleotide of claim 13. Instead, the claims encompass a broad scope of polynucleotides, which the specification fails to provide the necessary guidance for using. Therefore, one of skill in the art would not know how to use the entire scope of claimed polynucleotides. It is noted that nowhere does the examiner state that the claimed polynucleotide must encode a functional polypeptide. However, the specification clearly does not teach how a skilled artisan is use the entire scope of claimed polynucleotides, including those that encode non-functional polypeptides. Instead, the specification teaches only a single working example of the claimed polynucleotide – SEQ ID NO:2, encoding a polypeptide asserted to have phosphate transport activity. The specification provides no further guidance for using those polynucleotides that encode non-functional polypeptides or those polypeptides having function other than the asserted phosphate transport activity. Furthermore, the specification provides no

teachings as to how to interpret the results of an expression analysis for toxicology testing. In the instant case, the specification merely provides a starting point from which a skilled artisan can perform further experimentation in order to make and use the entire scope of claimed polynucleotides. At most the specification provides a description that will enable a skilled artisan to *attempt to discover* how to make and use the claimed invention. Therefore, as demonstrated by Factors of *In re Wands* as set forth above, undue experimentation would be required to make and use the entire scope of claimed polynucleotides.

Beginning at the middle of page 46 of the appeal brief, appellants argue the examiner's assertions that nucleic acid modifications may alter an encoded protein's function are limited to those polynucleotides are limited to fragments of a polynucleotide consisting of SEQ ID NO:2 and that a skilled artisan would know how to make and use these fragments. Appellants argue that the claimed polynucleotides are enabled as hybridization probes. Appellants' arguments are not found persuasive.

The nucleic acids of claims 13, 57, and 58 are not limited to fragments of a polynucleotide consisting of SEQ ID NO:2 as asserted by appellants. Instead the scope of the claimed polynucleotides encompasses *all* polynucleotides *comprising* fragments of SEQ ID NO:2. Appellants argue the claimed polynucleotide variants and polynucleotides comprising fragments of SEQ ID NO:2 may be used as hybridization probes, which it is noted is a non-specific utility as any nucleic acid can be used as a hybridization probe. However, it is unclear as to what further use the polynucleotides would be as hybridization probes and an endless amount of experimentation is required to determine the hybridization conditions and those nucleic acids that would hybridize under such conditions. In the instant case, the specification provides working guidance for only using SEQ ID NO:2 as a hybridization probe. The specification fails to provide guidance regarding the use of those polynucleotide variants and polynucleotides comprising fragments of SEQ ID NO:2 as hybridization probes and fails to provide direction for those nucleic acids that one would detect using the claimed polynucleotides. In this case, the specification merely provides a starting point from which a skilled artisan can perform further experimentation in order to make and use the entire scope of claimed polynucleotides as hybridization probes, which does not constitute an enabling disclosure.

Beginning at the middle of page 47 of the appeal brief, appellants argue the examiner would require a precise knowledge of the biological functions of polypeptides encoded by the claimed polynucleotides in order to satisfy the enablement requirement. Appellants argue all that is necessary to satisfy the enablement requirement is that a skilled artisan would reasonably understand how to make and use the claimed invention. Appellants argue that the references cited by the examiner show only that functional prediction cannot be made with 100% accuracy and that the references demonstrate that a skilled artisan would believe such predictions are reasonably accurate. Appellants' arguments are not found persuasive.

The issue is not whether functional annotation is reliable – as argued at great length by appellant – but whether appellant has enabled the entire scope of the claimed polynucleotides. However, in order to fully respond to appellants' arguments, it is noted that nowhere does the examiner state that the knowledge of the biological function(s) of encoded polypeptides is required to satisfy the enablement requirement. Instead, the examiner notes that one of the disclosed uses of the claimed polynucleotide is for protein expression and nowhere does the specification provide guidance as to how to make and use those encoded polynucleotides encoding polypeptides having function other than the asserted phosphate transport activity, i.e., non-functional polypeptides and polypeptides having a biological activity other than phosphate transport. Such polynucleotides are clearly encompassed by the instant claims and thus, undue experimentation would be required for a skilled artisan to make and use the entire scope of claimed polynucleotides – see particularly the analysis of the claims according to the Factors of *In re Wands* as set forth above detailing the broad scope of the claims, the lack of guidance and working examples, the high degree of unpredictability as evidenced by the prior art, and the amount of experimentation that is clearly undue in view of this analysis. Appellants attempt to apply the generalized teachings of Brenner et al. (1998) and Bork in arguing that there is a reasonable predictability of functional assignment based on sequence alone. As stated numerous times above, neither of these references applies to the instant case. The study of Brenner et al. (1998) does not relate to functional annotation and the results of Bork (*Genome Res* 10:398-400) are questionable as to their reliability.

At the bottom of page 48 of the appeal brief, appellants argue the use of the SCOP database in the study of Brenner et al. (1998) makes the general rules obtained by Brenner et al. (1998) more reliable. Appellants argue that since the reference database of Brenner et al. contains only proteins which have been fully characterized, any general findings are robust and reliable. Appellants argue the rules derived by Brenner et al. are ideal for addressing a situation such as this. Appellants argue the rules derived by Brenner et al. for identifying homology between proteins can be used to other less characterized proteins. Appellants argue that if it were necessary to characterize a protein before it was analyzed, then there would be no need for such analysis. Appellants argue there is no need for empirical determination or determination of 3-D structure of a protein to apply the general rules of Brenner et al. (1998). Appellants argue that it is not necessary for functional assignment of a protein to be absolutely correct to satisfy the enablement requirement. Appellants' argument is not found persuasive.

It is noted that the study of Brenner et al. (1998) has been conducted to identify distant evolutionary homology using sequence comparison algorithms. Nowhere does Brenner et al. state their results can be extrapolated for use in predicting functional homology. Clearly the study by Brenner et al. (1998) does not relate to the accuracy of functional assignment based solely on sequence homology. As stated numerous times above, appellants quote a portion of Brenner et al. (1998) out of context in an attempt to use these teachings to inappropriately support their argument. Furthermore, even assuming *arguendo* that the teachings of Brenner et al. (1998) were applicable to the instant case – which clearly they are not – it is unclear as to whether the results of Brenner et al. (1998) would be applicable to functional assignment of uncharacterized proteins as Brenner et al. (1998) limit their results to the database used in the study, which comprises proteins with known function and three-dimensional structures. Brenner et al. (1998) clearly state, "30% identity is a reliable threshold for this database" and that, "40% is a reasonable threshold, for a database of this particular size and composition" (underline added for emphasis). Appellants argue that other homologous proteins sharing percentage identity or portions of sequence with SEQ ID NO:2 or a nucleic acid encoding SEQ ID NO:1 would have the asserted phosphate transport activity based on the teachings of Brenner et al. (1998). However, as the teachings of Brenner et al. (1998) clearly do not apply to the instant case, and as evidenced by the prior

art, it is highly unpredictable as to whether a homologous polynucleotide or a polynucleotide encoding a homologous protein as encompassed by the claims would have phosphate transport activity – particularly in view of the broad scope of claimed polynucleotides.

At the bottom of page 49 of the appeal brief, appellants argue that, contrary to the examiner's assertions, the use of sequence comparison to predict protein function is supported by Bork (Genome Research 10:398-400) who allegedly discloses a 70% accuracy rate in bioinformatics-based predictions and a 90% accuracy rate when predicting functional "features". Appellants argue that even if the numbers of Bork are "crude estimates" and "overestimates", they are nonetheless Bork's best estimates for predicting accuracy. Appellants argue Bork's numbers were still the best test sets available in the literature, and are indicative of the state of the art at that time. Appellants argue that the reference of Bork supports the notion that a skilled artisan would reasonably understand how to make and use the claimed polynucleotide variants. Appellants' arguments are not found persuasive.

It is noted that the reference of Bork does not remove the high degree of unpredictability that is inherent in mutating or altering a protein-encoding polynucleotide. Bork clearly states gene annotation has a "considerable" error rate (page 399, middle column). Appellants' arguments fail to demonstrate that a high degree of unpredictability does *not* exist when one alters or varies a protein-encoding polynucleotide. As demonstrated by Factors of *In re Wands* as set forth above, undue experimentation would be required to make and use the entire scope of claimed polynucleotides.

Beginning at the top of page 50 of the appeal brief, appellants argue the quantitative criteria of Brenner et al. (1998) and Bork's estimates of accuracy demonstrate that the polypeptide variants recited by the claims would retain the function of NAPTR. Appellants argue the degree of unpredictability is not so high as to preclude a skilled artisan from believing that a mutant polypeptide would not retain the activity of the reference polypeptide. Appellants' arguments are not found persuasive.

It is noted that one of skill in the art recognizes - as evidenced by Broun et al., Seffernick et al., and Gerlt et al. - the teachings of Brenner et al. (1998) and Bork do not remove the high degree of unpredictability that is inherent in mutating or altering a protein-encoding polynucleotide. Appellants' arguments fail to demonstrate that a high degree of unpredictability does *not* exist when one alters or

varies a protein-encoding polynucleotide. The specification has provided no guidance as to those encoding nucleotides that are necessary (conserved) for encoding a protein having phosphate transport activity and those that are not or those encoding nucleotides that may be modified, resulting in the generation of a polypeptide having a novel, undesired, activity. As demonstrated by Factors of *In re Wands* as set forth above, undue experimentation would be required to make and use the entire scope of claimed polynucleotides.

Beginning at the middle of page 50 of the appeal brief, appellants argue the references of Broun et al. and Seffernick et al. do not support the examiner's assertion that amino acid modifications can alter protein function. Addressing the Broun et al. reference, appellants argue the mutations as taught by Broun et al. do not completely alter the function of the desaturase to a hydroxylase as the mutant retains some desaturase activity. Appellants argue that Broun et al. note that a small number of amino acid substitutions account for the functional divergence of a number of enzymes, and conclude from this remark by Broun et al. that this supports the notion that most amino acid substitutions have no effect or minimal effect on protein function. Appellants' arguments are not found persuasive.

It is noted that the reference of Broun et al. has not been cited in the rejection set forth in the examiner's answer due to the duplicative nature of the other cited references. The examiner acknowledges the mutant desaturase of Broun et al. maintains desaturase activity. However, the desaturase of Broun et al., prior to mutation exhibited no hydroxylase activity – only upon mutation did the mutant desaturase of Broun et al. exhibit hydroxylase activity. While the four mutations of Broun et al. did not *completely* convert the desaturase activity to a hydroxylase activity, the mutations as taught by Broun et al. nonetheless led to the generation a novel activity for their desaturase, thus providing support for the unpredictability of modifying an encoding nucleic acid. The specification has provided no guidance as to those encoding nucleotides that are necessary (conserved) for encoding a protein having phosphate transport activity and those that are not or those encoding nucleotides that may be modified, resulting in the generation of a polypeptide having a novel, undesired, activity.

Beginning at the bottom of page 50 of the appeal brief, appellants address the reference of Seffernick et al., arguing the proteins having distinct functions as taught by Seffernick et al. belong to

same enzyme superfamily. Appellants argue there is a member of this superfamily that catalyzes both deamination and dechloronation with triazine ring substrates. Appellants conclude from this that the 98% identity between the proteins of Seffernick et al. "correctly predicts their functional similarity and their membership in a common enzyme family". Appellants argue this example demonstrating the difficulty in predicting function does not contradict Bork et al. who allegedly teach that protein function is accurately predicted by sequence homology methods. Appellants argue in the Seffernick et al. example, sequence homology correctly assigns the proteins to a particular enzyme family whose members share similar enzyme activities. Appellants argue that Seffernick et al. do not contradict the evidence that one of skill in the art would reasonably conclude that NAPTR could be used in the same manner as the NPT1 phosphate transporter. Appellants' arguments are not found persuasive.

It is noted that while the enzymes of Seffernick et al. belong to the same superfamily, the enzymes nonetheless have distinct functions. It is noted that, in the instant rejection, the reference of Seffernick et al. has been provided to support the unpredictability that the claimed variant nucleic acids will encode polypeptides having the identical function to SEQ ID NO:1 and not that SEQ ID NO:1 has an identical function to NPT1. Appellants' argument attempts to imply that the enzymes as taught by Seffernick et al. are functionally similar by belonging to the same superfamily of enzymes and is allegedly in line with the teachings of Bork. However, the enzymes are *not* functionally similar as evidenced by the title of the reference of Seffernick et al. – "Melamine Deaminase and Atrazine Chlorohydrolase: 98 Percent Identical but Functionally Diverse". Each of the enzymes – while being 99% identical at the encoding nucleic acid level - exhibits a distinct function and neither uses the other's substrate. This clearly contradicts the teachings of Bork. The mere inclusion of enzymes within a superfamily is not indicative of their functional similarity or divergence. One of skill in the art recognizes that homologous members of a superfamily may have diverse functions as evidenced by Gerlt et al. teach that "even within homologous families of a single superfamily, the level of sequence similarity required for reliable prediction of function from sequence cannot be specified with confidence" (page 0005.2, right column, bottom to page 0005.3, left column, top). Gerlt et al. further teach their results "illustrate that mechanistic diversity does not require a large significant divergence in sequence, and underscore that high levels of

sequence identity do not 'guarantee' the same enzymatic function" (page 0005.3, right column, middle), thus contradicting the teachings of Bork et al. and Brenner et al. (1998). Collectively, the references of Broun et al., Seffernick et al., Brenner (1999), and Gerlt et al. provide evidence for the high degree of unpredictability that the claimed variants could be used in the same manner as the NPT1 phosphate transporter.

Beginning at the bottom of page 51 of the appeal brief, appellants address the reference of Gerlt et al. arguing that even though the teachings of Gerlt et al. are correct, this does not negate that structural homology is a reasonably reliable indicator of functional homology. Appellants argue that despite the teachings of Gerlt et al., a skilled artisan would understand the estimates of Bork represent the state of the art in evaluating sequence analyses and would consider these reasonably reliable. Appellants argue Gerlt et al. does not contradict Bork and Brenner et al. (1998). Appellants argue the examiner has not shown that the degree of unpredictability is so high that a skilled artisan would reasonably doubt how to make and use the claimed invention. Appellants argue the examiner insists that there must be no margin for error in functional annotation in order for the invention to meet the enablement requirement. Appellants' arguments are not found persuasive.

It is noted that the reference of Bork does not remove the high degree of unpredictability that is inherent in mutating or altering a protein-encoding polynucleotide. Appellants' arguments fail to demonstrate that a high degree of unpredictability does *not* exist when one alters or varies a protein-encoding polynucleotide. The examiner disagrees with appellants' statement that the examiner insists that there must be no margin for error in functional annotation in order for the invention to meet the enablement requirement. The issue is not whether functional annotation is a reliable method, instead, the issue at hand is whether appellant has enabled the entire scope of claimed polynucleotides. It is the examiner's position that appellant has not enabled the entire scope of the invention for those reasons stated above. Neither the specification nor the prior art provides guidance as to those encoding nucleotides that are necessary (conserved) for encoding a protein having phosphate transport activity and those that are not or those encoding nucleotides that may be modified, resulting in the generation of a polypeptide having a novel, undesired, activity. As demonstrated by Factors of *In re Wands* as set forth

above, undue experimentation would be required to make and use the entire scope of claimed polynucleotides.

Beginning at the top of page 53 of the appeal brief, appellants argue the teachings of Seffernick et al. recognize that functional assignments based on >50 % sequence identity are considered to reasonably sound and that proteins with >98% sequence identity catalyzing different reactions is highly exceptional. Appellants allege that these statements by Seffernick et al. do not contradict the findings of Bork et al. who, appellants allege, teach that in general, sequence homology is an accurate method for assigning biological function. Appellants' arguments are not found persuasive.

Appellants' statement by Seffernick et al. regarding >50% sequence identity has been mischaracterized. In fact, Seffernick et al. teach their result of identifying two proteins with >98% identity and having distinct functions "underlies current genome annotation efforts where functional assignments based on >50 % sequence identity are considered to reasonably sound" (page 2409, left column, middle) and thus provides additional support for the uncertainty in assigning function based on structural identity alone. While it is acknowledged that Seffernick describe their findings as "highly exceptional", this reference nonetheless provides evidence for the unpredictability in assigning function to a variant based solely on sequence. Regarding the reference of Bork, it is noted that appellants have ignored the teachings of Bork, particularly the footnote to Table 1 of Bork, which states that the evidence provided is a crude estimate and that "numbers in Table 1 are often overestimates because the test sets used are usually not representative of all sequences". Furthermore, the state of the prior art suggests a high degree of unpredictability in assigning function based on sequence alone. It is the examiner's position that appellant has not for those reasons stated above. Neither the specification nor the prior art provides guidance as to those encoding nucleotides that are necessary (conserved) for encoding a protein having phosphate transport activity and those that are not or those encoding nucleotides that may be modified, resulting in the generation of a polypeptide having a novel, undesired, activity. As demonstrated by Factors of *In re Wands* as set forth above, undue experimentation would be required to make and use the entire scope of claimed polynucleotides.

Beginning at the bottom of page 53, appellants argue the statement by Bork, that "predicting the function of a polypeptide... ...by sequence database searches has a considerable error rate" does not negate the "fact" that there is a 90% accuracy rate for the prediction of functional "features" by homology as disclosed by Bork. Appellants argue that, at most, errors can occur in functional assignment. Appellants argue that Bork does not show that errors do not occur, but it allegedly quantifies the error rate at 10%. Appellants argue that the cited references do not contradict that such assignment methods are accurate more than not and, as such, one of skill in the art would reasonably conclude that NAPTR possesses the function of the family of phosphate transporter proteins. Appellants' arguments are not found persuasive.

The cited references used in the instant rejection have been applied to demonstrate the unpredictability of assigning function to the nucleic acid variants and nucleic acids comprising fragments as claimed and not to assigning function to NAPTR as asserted by appellants. Regarding the reference of Bork, again it is noted that appellants have ignored the teachings of Bork, particularly the footnote to Table 1 of Bork, which states that the evidence provided is a crude esti3mate and that "numbers in Table 1 are often overestimates because the test sets used are usually not representative of all sequences". Bork have not established a "fact" of 90% accuracy rate for the prediction of functional "features" by homology. One of the references Bork relies on in establishing this alleged "fact" is that of Brenner et al. (1998). Brenner et al. (1998) teach an error rate of "at least 8% for the 340 genes annotated", provides evidence for why this error rate must be greater, and states, "the true error rate must be greater than these figures indicate". Thus, appellants characterization of the reference of Bork as statements of "fact" is misleading as Bork has not established a "fact". To the contrary, as evidenced by Broun et al., Seffernick et al., Brenner (1999), Gerlt et al., and Scott et al., the art recognizes the unpredictability in assigning function based on sequence identity alone. It is the examiner's position that appellant has not for those reasons stated above. Neither the specification nor the prior art provides guidance as to those encoding nucleotides that are necessary (conserved) for encoding a protein having phosphate transport activity and those that are not or those encoding nucleotides that may be modified, resulting in the generation of a polypeptide having a novel, undesired, activity. As demonstrated by Factors of *In re*

Wands as set forth above, undue experimentation would be required to make and use the entire scope of claimed polynucleotides.

Beginning at the middle of page 54 of the appeal brief, appellants argue the examiner has failed to demonstrate that a skilled artisan could not make and use the claimed polynucleotides. Appellants argue the examiner has only provided isolated examples in which mutations can sometimes result in a shift of the biological activity of a polypeptide. Appellants argue the references of Brenner et al. (1998) and Bork present general findings related to the accuracy and reliability of sequence analysis methods. Appellants argue the cited references have no bearing on the ability of a skilled artisan to make the relevant polynucleotides and their encoded polypeptides which already exist in nature, without undue experimentation. Appellants' arguments are not found persuasive.

As stated above, neither Brenner et al. (1998) or Bork are related to the instant case. In regards to the issue of enablement, it is noted that the claims are not so limited to naturally-occurring nucleic acids or nucleic acids encoding naturally-occurring amino acid sequences. Instead, claims 13, 48, 57, and 58 are drawn to polynucleotides *comprising* fragments of SEQ ID NO:2 or variants thereof – there is no limitation provided in these claims that the nucleic acids or encoded proteins be naturally-occurring. As demonstrated by Factors of *In re Wands* as set forth above, undue experimentation would be required to make and use the entire scope of claimed polynucleotides. The cited references of Broun et al., Seffernick et al., Brenner (1999), Gerlt et al., and Scott et al. provide the state of the prior art, which demonstrates the high degree of unpredictability of making one or more mutations in an encoding nucleic acid sequence with an expectation of obtaining an encoded protein having a desired biological activity. As the prior art is replete with examples of mutations altering the function of a protein, the examiner has selected the cited references as representative and are not "isolated examples" as asserted by appellants.

Beginning at the bottom of page 54 of the appeal brief, appellants argue the examiner's arguments ignore the ability of a skilled artisan to make and use the claimed polynucleotides and provide examples in support thereof. Appellants argue the examiner has provided no arguments concerning the lack of enablement of the claimed polynucleotides. Appellants argue a skilled artisan could make and use

the claimed fragments without undue experimentation, provided the specification and the state of the art and provide examples in support thereof. Appellants argue that, contrary to the standard set forth in *In re Marzocchi* (169 USPQ 367, 369 (CCPA 1971)), the examiner has failed to provide reasons why one would doubt that the guidance provided by the specification would enable a skilled artisan to make and use the claimed polynucleotides or arrays comprising nucleic acids hybridizable to portions of the recited polynucleotides. Appellants conclude that a *prima facie* case for non-enablement has not been established for the clamed nucleic acids. Appellants' arguments are not found persuasive.

It is noted that the nucleic acid of the array of claim 48 is not so limited to a nucleic acid hybridizable with at least 30 contiguous nucleotides of a polynucleotide comprising SEQ ID NO:2. Instead, the claim is so broad as to encompass an array comprising *all* nucleic acid molecules comprising a first oligonucleotide or polynucleotide that specifically hybridizes with at least 30 contiguous nucleotides of a target polynucleotide of claim 12, which itself is so broad as to encompass variants having at least 90% identity to SEQ ID NO:2. It is noted that the function of the nucleic acids comprising fragments of SEQ ID NO:2 is not limited to a hybridization probe and, from the specification, it appears that an intended use of the claimed nucleic acids is for protein expression (see for example, page 14, lines 19-21, and page 41, lines 7-19 of the instant specification). The claims encompass nucleic acids encoding variants and nucleic acids comprising fragments that have the asserted phosphate transport activity in addition to variant polypeptides that are non-functional or exhibit a function other than the asserted phosphate transport activity. While techniques for isolation of nucleic acids encoding variants are known in the art, other than a method for screening those nucleic acids encoding polypeptides having the asserted phosphate transport activity, the specification provides no additional guidance in the form of assays for identifying those encoded proteins having activities other than the asserted phosphate transport. There are no working examples of variants of the SEQ ID NO:2 or nucleic acids encoding variants of SEQ ID NO:1. Furthermore, there is no guidance provided in the specification as to what *all* nucleic acids encoding variant polypeptides can be used for – particularly those variants encoding non-functional polypeptides. Appellants argue that polynucleotides encoding non-functional polypeptides can be used to detect polynucleotides encode NAPTR. However, the claims are not limited to those

polynucleotides having substantially similar structures that would be so useful – see for example, the polynucleotide of claim 13. Instead, the claims encompass a broad scope of polynucleotides, which the specification fails to provide the necessary guidance for using. Therefore, one of skill in the art would not know how to use the entire scope of claimed polynucleotides. It is noted that nowhere does the examiner state that the claimed polynucleotide must encode a functional polypeptide. However, the specification clearly does not teach how a skilled artisan is use the entire scope of claimed polynucleotides, including those that encode non-functional polypeptides. Instead, the specification teaches only a single working example of the claimed polynucleotide – SEQ ID NO:2, encoding a polypeptide asserted to have phosphate transport activity. The specification provides no further guidance for using those polynucleotides that encode non-functional polypeptides or those polypeptides having function other than the asserted phosphate transport activity. Furthermore, the specification provides no teachings as to how to interpret the results of an expression analysis for toxicology testing. In the instant case, the specification merely provides a starting point from which a skilled artisan can perform further experimentation in order to make and use the entire scope of claimed polynucleotides. At most the specification provides a description that will enable a skilled artisan to *attempt to discover* how to make and use the claimed invention. As demonstrated by Factors of *In re Wands* as set forth above, undue experimentation would be required to make and use the entire scope of claimed polynucleotides.

Double Patenting Rejection

Beginning at the top of page 56 of the appeal brief, appellants acknowledge the obviousness-type double patenting rejection of claims 3-7, 9, 10, 12, and 57. Appellants request that the requirement for submission of a Terminal Disclaimer be held in abeyance until there is an indication of allowable subject matter. The examiner acknowledges appellants' request.

It is noted that at pages 43-44 appellants summarize their remarks presented at pages 35-43 of the appeal brief. It is further noted that at page 56 appellants provide concluding remarks. As these remarks

merely summarize arguments previously presented by appellants in the appeal brief, the examiner has not responded to these remarks.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

David J. Steadman, Ph.D.
October 31, 2003

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merely summarize arguments previously presented by appellants in the appeal brief, the examiner has not responded to these remarks.

For the above reasons, it is believed that the rejections should be sustained.

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